IN SEARCH OF AN AIDS CURE

California and the Federal Governments' Struggle
To Promote Innovation in AIDS Drugs, Vaccines and Therapies

by Roger Lane Carrick and James T. O'Reilly

Working Manuscript of March 24, 1989
Copyright 1989
All Rights Reserved
# TABLE OF CONTENTS

Introduction -- AIDS -- A Terrifying New Idea

A Review of the Search for an AIDS Cure: The Crucial Role of Politics, Policy and Government in Understanding Why We Search and Where We Are

1. Background of the Struggle: The FDA's Handling AIDS-Related Drugs

2. The California "Fresh Start" Experience
   2.1 The West Hollywood Meeting
   2.2 The Background on California's Response to AIDS
   2.3 Drug Testing and Licensing Become the Key Concern
   2.4 The Clash over Drug Testing and Licensing Philosophy
   2.5 The California AIDS Drug Testing Innovation
   2.6 California's Existing Sherman Food and Drug Act
   2.7 The Van de Kamp Proposal
   2.8 The Debate Over the Van de Kamp Proposal
   2.9 The Development of Legislation
   2.10 The California "Fresh Start" Legislation
   2.11 The Opposition to Van De Kamp's Proposal
   2.12 The Legislature's Actions
   2.13 The Feinstein Opposition
   2.14 Governor Deukmejian's View
   2.15 The Post-Approval Perspective
   2.16 California's Challenge to FDA

3. The Response to AIDS: Regulatory Evolution, Not Revolution
4. **A Scientific Introduction to AIDS** .................................................. 52
   4.1 Overview .................................................. 52
   4.2 Molecular Biology of HIV Infection .................................. 53
   4.3 Chronological Review of AIDS Research .................................. 56
   4.4 Current Statistics and Trends of AIDS As a Disease .......... 58

5. **A Summary of Current Research Directions for AIDS-Related Drugs** .................................................. 64
   5.1 Background on Federal Research Efforts .................................. 64
   5.2 Antiviral Drugs .................................................. 66
   5.3 Alpha Interferon and Kaposi's Sarcoma .................................. 68
   5.4 Antiviral Drugs: The Promising Few .................................. 69
   5.5 Vaccines .................................................. 75
   5.6 Drugs for Pneumonia and Infections .................................. 80
   5.7 Drugs for Cancer Symptoms .................................. 83
   5.8 HIV Detection Kits .................................................. 84
   5.9 Nutrition and Maintenance .................................................. 85
   5.10 Problems of Research .................................................. 86

II. **The Search for an AIDS Cure Today - o The What and How of the Search for AIDS Drugs and Vaccines in America** .................................................. 89

6. **How Government Regulates Health Products** .................................................. 89
   6.1 Principles of Categorization: when is a Product a Drug .................................. 89
   6.2 "Drugs" and "New Drugs" Defined .................................................. 90
   6.3 "Medical Devices" Defined .................................................. 92
   6.4 Vaccines and Biologics Defined .................................................. 93
   6.5 Detection Assays and Diagnostics .................................................. 95
   6.6 Medical Foods .................................................. 95
   6.7 Orphan Drugs .................................................. 96

7. **The Approval Process for Drugs - Overview** .................................................. 98
   7.1 FDA's Operation of the New Drug Application Requirements .................................. 98
   7.2 Legal Requirements for New Drug Application Approval .................................. 100
   7.3 What is "Safe?" .................................................. 102
   7.4 What is "Effective?" .................................................. 103
   7.5 Comparative or Subjective Claims .................................................. 105
   7.6 Chronology of an Approved Drug .................................................. 106
   7.7 Principle Suggestions for Change .................................................. 113

8. **Stages of the Approval Process** .................................................. 115
   8.1 Origins in the Bench Research .................................................. 115
   8.2 The Animal Study Phases .................................................. 118
CHAPTER 1
BACKGROUND OF THE STRUGGLE:
THE FDA'S HANDLING AIDS-RELATED DRUGS

Brief Historical Sketch of Drug and Vaccine Regulation

Federal control over new and experimental drug products has a history of more than a half-century. The entity that we know today as the Food and Drug Administration ("FDA") was originally established around the turn of the century as the Department of Agriculture's Bureau of Chemistry. The FDA became a separate agency in 1927, at which time it was renamed the Food, Drug and Insecticide Administration. The FDA acquired its current shape and identity during the New Deal era of the 1930's.

Congress recently formalized FDA's structure and command roles in the 1988 Health Omnibus Programs Extension Act. The Commissioner of Food and Drugs, the government official in charge of the FDA, will in the Bush Administration be appointed by the President and confirmed by the U.S. Senate, giving the Congress greater control over the FDA. Prior to the 1988 change, the FDA Commissioner was just one of many officials appointed by the Secretary of the Health and Human Services Department.

Congress has historically struggled with the problem of human drug products and the degree of their government control. The struggle was most evident in the five year Congressional
debate during the New Deal era of President Franklin D. Roosevelt. Major social control decisions made during that time are taken for granted today, such as mandatory contributions to social security, full disclosure of securities risks, bank insurance, and other major programs. Congress could not decide during the legislative sessions of 1933-1938 precisely what federal control of drug development was appropriate.

Then, as often happens, a coincidental crisis while legislation was pending produced the outcry which led to the modern Food and Drug Administration control of drugs. A mistake in formulation of a new sulfa drug caused the prolonged, painful deaths of 93 persons, many of them children, by poisonous effects of the drug's liquid dissolution ingredient. Congress rapidly passed a mandatory product approval requirement which would apply for every new drug marketed in the United States, and Congress also empowered the Food and Drug Administration to issue drug approvals or denials based on evidence of safety presented by drug manufacturers.

The FDA's powers of approval were tempered in the law. Administrative procedures for the review of an application within a defined time period and several limitations on authority of the FDA were included in the 1938 Act and its 1962 amendments. For example, FDA is required to hold hearings upon the withdrawal of any approved new drug application, with certain preconditions and limitations on this opportunity for hearings. A final denial of the application could be appealed to the courts. Rapid
withdrawal is not easy to impose over the objection of the drug sponsor. FDA was not unlimited in its powers to control a new drug once approved.

In 1962, the law again was amended to cure perceived flaws after the Thalidomide drug tragedy. Between 1938 and the 1962 amendments, FDA approval meant that the drug was "safe", but not that it necessarily was "effective". The 1962 amendments dramatically increased the hurdles for drug approval applicants to overcome. They now would need at least two scientifically controlled, statistically valid studies proving that the drug product was effective against each of the disease conditions for which the sponsor sought to sell it. This new efficacy standard would become the measurement against which all new drugs would be tested. Statistical proof of benefits in patients became the test of success or failure for a new drug.

Regulatory control of a product's safety -- the only control under the 1938-1962 approval system -- is much easier, much faster and far less costly than supervision of product effectiveness. Animal studies of toxicity and human studies in a relatively small number of patients can demonstrate that the drug is not acutely harmful when ingested. (Cancer and other chronic effects of a drug may be much more difficult to detect, of course.) Proof of efficacy requires scientific judgment, statistics, and full evaluation of a well defined patient population. The more fluid or novel the disease, the more difficult would be the proof of efficacy. For a fatal viral
infection like AIDS, prolonged survival is the result which proves the drug's effectiveness.

FDA's control of efficacy carries with it the power to deny entry into the market of safe and beneficial drugs which have not yet been shown by statistical data to perform better than a "placebo" (inactive look-alike) in human testing. If a new drug is safe but only may be effective, FDA can hold the product out of commercial distribution until full sets of human patient tests ("clinical trials") demonstrate that the drug actually delivers a benefit against the labeled condition.

In the case of a drug for persons infected with the Human Immuno-Deficiency Virus ("HIV"), therefore, FDA must apply the Congressional requirements for both safety and effectiveness. The FDA has authority to deny approval even if an HIV-related drug is absolutely safe, until adequate statistical data of use of that drug in human patients proves that the drug is effective against HIV, Kaposi Sarcoma, or other conditions referenced on the label.

Congress has also raised the risks of not complying with the agency's directives. The law has strengthened the FDA's enforcement authority. Though a new drug marketer may believe that its product is not required to apply for FDA approval, FDA can seize the product, or could in exceptional cases seek prosecution by federal law enforcement officials, if the drug maker failed to remove the alleged "new drug" from the market. It is a little-known fact that new drug cases can result in jail
terms as well as very large corporate or individual fines without any proof of intent to violate the law. The Supreme Court has consistently held that FDA prosecutions for drug manufacturing violations do not require any proof of criminal intention. This makes it easier to convict the unwitting criminal defendant, such as the drug manufacturer's president who had a "responsible relationship" to the decision to market an HIV drug without getting FDA approval. The sanctions of criminal prosecution, fines and injunctions tend to create a special respect for FDA's requirements.

Criticism of the FDA

Criticism of the FDA's lengthy and difficult review of pharmaceutical products did not begin with the AIDS controversy. Industry, medicine and the press complained vigorously in the 1970's that the FDA took much longer than its counterpart agencies in comparable industrialized countries to review and license drugs. According to a major General Accounting Office report to Congress in 1980, drug approval agencies in Norway, Canada, the United Kingdom and Switzerland all moved more quickly than the FDA's average eight to ten years from the initial research application through to licensing, including a twenty month lag in the average time from the submission of a New Drug Approval request to FDA's final approval for sale of the product. Criticism of this glacial pace led the drug manufacturing companies in the United States to lobby Congress
into adopting in 1984 a specific extension in the exclusivity of a patent right for pharmaceutical product innovations to make up for the virtually guaranteed delay period before FDA approval.

But the Wall Street Journal perhaps echoed best the structural conflict in the FDA's role of regulating drug products intended to alleviate American illness while not contributing to iatrogenic creation of health problems. In editorials beginning in 1986 through 1988, the Wall Street Journal focused on the tremendous time lags that have occurred in drugs reaching American markets since 1962. That year is critical, for while the FDA has been charged since 1938 with assuring that a drug is safe, the Kefauver amendments in 1962 mandated the use of clinical trials to prove that a drug is effective before it is made available to the public.

The 1962 amendments were prompted by the public outcry over the baby-deforming sedative thalidomide, which while licensed for sale in Europe, nonetheless proved dangerous in use. The resulting process of proving that a drug is both safe and effective are undoubtedly responsible for the long testing, review and licensing process for drugs in America today. Indeed, one major study found that in 1949, some 559 new products were licensed, with an average regulatory review time of around seven months. Yet in 1969, only 83 new drug products reached the American marketplace, and the review process time had tripled.

While this public perception that the FDA stood between quacks and the public is one of its strongest assets, this
propensity to move with deliberate speed in a cautious, almost suspicious manner with regard to new drugs and their nominal health claims clearly weighed negatively on the FDA in its matchup with AIDS. Two major commentaries on the history of governmental efforts generally to deal with AIDS have underscored the human drama amidst the bureaucratic hurdles that mark this debate over the AIDS effort.

In And The Band Played On (St. Martin's Press, 1987), author/journalist Randy Shilts explored the human drama of the epidemiological sleuthing behind the formal resolution of the HIV virus as the culprit behind the AIDS epidemic, as set against the human pathos of AIDS' impact in the community.

In The AIDS Bureaucracy (Harvard University Press, 1988), Sandra Panem of the Alfred P. Sloan Foundation documented in excruciating detail the glacial pace of budgetary and bureaucratic decision-making in response to the AIDS crisis.

The conventional wisdom reflected in editorial commentary and scholarly books grew from the popular critique that the Federal Government was unresponsive to the horrific finality of AIDS as a disease, particularly given the prevalence of this disease (at least initially) in the gay community. Amid this backdrop of criticism and social commentary, the FDA was almost assigned the "bad guy" role as the next agency dealing with the HIV epidemic, following the initial documentation of the epidemiology of the disease by the Center for Disease Control and then the identification of the HIV virus by the French and
researchers at the National Cancer Institute. While the FDA's historical concern for quackery was commendable in the view of gay activists and medical clinicians, desperate AIDS victims and their doctors argued that they deserved a heightened awareness of the devastating consequences of AIDS, that they deserved a more human response than traditional scholarly debate allowed, and that agonizingly deliberate scientific and regulatory documentation of a drug's safety and efficacy did not respond to the human reality of rapid disease progression.

Newspaper opinion pages increasingly reflected this view, including particularly dramatic statements headlined as "The FDA's Callous Response" in the New York Times, "Uproar over AIDS Drugs" in Newsweek in the spring of 1987, and "Foot Dragging on AIDS" in the Los Angeles Times in the summer of 1987, more traditional editorial responses, such as U.S. News and World Report's "Putting Drugs on a Fast Track May Hurt Research -- and Increase Suffering: The Government Bends to AIDS Victims' Pleas," were overwhelmed.

Indeed, this popular view appeared to be confirmed by yet another General Accounting Office report to Congress in the summer of 1987, wherein major national scientific researchers complained openly about the red tape and delays in both Federal AIDS research funding and in the translation of research on possible drugs into viable clinical trials.

By the fall of 1988, these cumulative criticisms of the FDA had reached massive proportions, including street
demonstrations before the FDA's headquarters in Rockville, Maryland, and derisive denunciations of the FDA in Newsweek magazine as "the FDA - the foot-dragging administration."

In response to this criticism, the FDA began beefing up in 1986 its medical staff officers who review new drug proposals. In November, 1987, the FDA reorganized the Center for Drugs and Biologics into two separate organizations called respectively the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research. According to the FDA's press report, this change was taken specifically to enhance the FDA's AIDS emphasis in drug reviews.

In its most widely heralded change, on January 14, 1988, FDA announced that any potential AIDS-related drug would receive a I-AA classification, the highest priority rating in the FDA drug review system. As evidence of the effectiveness of these types of changes, FDA defenders note that the first I-AA AIDS-related drug, zidovudine (AZT), was approved for clinical testing after only a five day FDA review, and was licensed for use after only 107 days of clinical trial. Indeed, the historical drug development and evaluation process, which had taken an average of 8 years from initial human testing under an "investigational new drug" process through final marketing approval, took only two years with AZT.

In light of these approaches, FDA announced at the end of 1987 that some 164 investigational new drug applications for AIDS-related therapies covering 85 separate drug products had
been reviewed by FDA, with 146 receiving approval for testing. Perhaps as many as 300 similar applications were pending or approved in late 1988.

The battle lines are thus clearly drawn in any discussion of the FDA and drug products, including AIDS-related drugs. The FDA is charged by law with being diligent and tough on proposed new drugs, including finding that these drugs are both safe and effective. At the same time, the drug sponsors are usually companies seeking profits through a federally-approved product, scientific researchers are seeking professional fame and glory by confirming in clinical trials their laboratory theories, while persons afflicted with a disease such as AIDS are desperately willing to try almost anything to preclude the only known outcome of AIDS - death. Because those afflicted with AIDS are a classic example of a community open to quacks, exploiters and cynical business practices, the regulatory conundrum is poignant. How do we regulate for safety without sacrificing current victims' health and maybe even their lives in hopes of reaching future therapies, cures or vaccines?

These are the toughest questions -- the why questions of health regulation. While we shall explore the nature of society's discussion of these questions in the next five chapters, this book is primarily designed to answer the how and what questions of how drugs will be regulated in the 1990's. The goal is to advance, not repeat, history.
CHAPTER 2

The California "Fresh Start" Experience

Section 2.1 - The West Hollywood Meeting

On the evening of May 18, 1987, a fateful conversation began as California Attorney General John Van de Kamp took a seat in an overstuffed chair in a West Hollywood living room to discuss with a group of gay community leaders a subject light years away from his usual battles against gangs, drug lords and toxic polluters. For two and one-half hours this law enforcement official, a public official whose integrity and commitment to impartial justice made him almost uniquely bland in a California climate of trendy, headline-seeking politicians, listened to six men and three women community activists talk about death and dying.

A lawyer who as a Lyndon Johnson Justice Department official had prosecuted Dr. Benjamin Spock for interfering with military conscription in the 1960's, Van de Kamp's bone-dry demeanor softened early in the evening as he listened to these activists' often heart-rending emotional reflections on their friends' struggles with AIDS. As Van de Kamp would later recall, "It was a cry of frustration ... one of the gloomiest evenings I've spent in a long time."
While deeply personal and emotional, this meeting of the innocuously named "Book Study Group" in David Mixner's living room marked a unique turning point in AIDS drug testing and licensing. Listening to gay activists like Jean O'Leary describe "a whole generation of men dying and going to die," Van de Kamp came away with a new perspective on AIDS. O'Leary's question - "Can't you help us do something?" - would echo in his subsequent California state policy initiative aimed at addressing the focal point of the evening: how can government speed-up the testing and licensing of AIDS-related therapeutic drugs and vaccines. This priority of California's gay activist community followed what they initially perceived to be more fundamental battles, particularly focusing on defeating the efforts of extremist groups to pass draconian political initiatives aimed at universal AIDS testing and subsequent quarantine of persons with AIDS. Following LaRouche's defeat, California's gay activist community moved to the offense, starting a systematic effort aimed at educating California politicians about the needs of the AIDS-affected community.

Section 2.2 The Background on California's Response to AIDS

Although the AIDS epidemic hit New York City first and hardest in terms of total AIDS cases in the United States, California government at both the state and local levels responded relatively quickly and with what were, in retrospect, dramatically high funding levels for AIDS-related activities. In
1982, the San Francisco Board of Supervisors allocated $1 million for municipal AIDS-related activities, less than one year after the first formal report on AIDS (in Los Angeles) was published. In May of 1983, this appropriation was doubled to $2.1 million, a figure which when combined with the 1982 appropriation exceeded the funds released to the entire country by the National Institutes of Health for extramural AIDS research by 1982.

California state politicians responded to the AIDS crisis in its early stages as well, beginning in 1983 with a requirement that local health officers report all AIDS cases. This action was followed in 1985 with a California law requiring that every blood bank and plasma center test its blood and blood products for the presence of the AIDS virus. The state also funded a network of state-sponsored Alternative Test Sites for free AIDS testing and counseling on how people could either avoid the AIDS infection or deal with a positive AIDS test. By mid-1986, the State of California had spent over $152 million on AIDS medical care and $23 million on AIDS research.

Eager California state legislators introduced 60 separate AIDS-related measures in 1987 alone, having passed 65 separate AIDS-related legislative initiatives in the years from 1982 through 1986. Unfortunately, paralleling the Congressional experience of forcing funds on a cautious President, the California Legislature initiated 63 of these bills in the face of a passive Governor, who nonetheless by 1986 had vetoed $30 million of the total funds passed by the California Legislature.
for AIDS-related programs. Though mirroring similar vetoes by the Governor of New York, the California Governor's actions seemed remarkably out of step with his state's legislative mood.

Indeed, while activists provided the initial focus and leadership, the explosion in press coverage and the emerging threat to the heterosexual community posed by AIDS created a climate in which by the spring of 1987 AIDS became Issue Number 1 across California. On May 10, 1987, the widely respected California Poll reported that AIDS had become the most important issue facing California, and that research for a cure should be the top priority for increased state financing. 73% of Californians polled indicated that California state spending on AIDS should be increased. The AIDS issue outpolled public education, drug abuse, and programs for the elderly, the perennial voter favorites for budget action along with crime-related expenditures. 69% of those polled indicated that AIDS was more important as a policy issue than improving public schools and reducing the spread of illegal drugs, the closest competitors to AIDS in the poll's results.

However, AIDS testing was very controversial. Seventy per cent of Californians indicated that they favored mandatory testing of prisoners for AIDS, a view that resulted in adoption by an initiative statute of just such a policy for prisoners by the California electorate in November, 1988. A relatively narrow majority of voters rejected at the same time universal testing for AIDS. The electorate has twice rejected initiatives on the
California general election ballot in 1986 and 1988 aimed at just such universal testing.

In the early summer of 1987, the people of California's top public policy priority was for fast, effective research on AIDS therapies and vaccines. Their emotional concerns grew stronger as an enormous volume of quantitative and financial information was introduced into local and state budget debates. The respected Senate Office of Research ("SOR") was estimating in the summer of 1987 that at least 300,000 Californians were infected with HIV, with over 8,000 confirmed cases of AIDS, of which more than 4,500 had already died. SOR predicted that by 1991, an estimated 50,000 Californians would be diagnosed with AIDS, resulting in 34,000 deaths. Such numbers would result in a range of medical care expenditures for AIDS care by 1991 of between $1.1 and 1.7 billion, of which as much as $450 million would be paid by taxpayers through the MediCal program. By 1991 the annual tab for AIDS-related medical care might explode to as much as $2 billion as the absolute number of terminal AIDS patients escalated, resulting in a cumulative economic impact in 1991 (e.g., loss of wages, future earnings and economic productivity) of as much as $16 billion lost to the state's economy. The demands for action mounted almost as rapidly as did the costs of AIDS.
Section 2.3 Drug Testing and Licensing Become the Key Concern

Yet the gay activist community knew that while education, counseling and testing were important issues, an essential element of the AIDS problem was as yet unaddressed. While activists worked hard for additional Federal and state scientific research dollars, only a trickle of new drugs appeared likely to make their way to AIDS victims. With only one drug - AZT - likely to be licensed in 1987, these activists were grimly determined to take up the challenge of slow, painstaking bureaucracies and their control over the actual release of drugs into the market.

This focus on testing and licensing of drugs was a relatively new development. As Van de Kamp learned that evening in West Hollywood, Jean O'Leary's group, the National Gay Rights Advocates, had recently filed suit against the Federal Food and Drug Administration ("FDA") and the National Institutes of Health in a desperate attempt to force faster approval of AIDS drugs for national testing among volunteers. This legal effort reflected a concern for the pace of national AIDS drug trials, which Congressional sponsors in 1986 and 1987 had suggested would involve up to 10,000 persons, but which in fact by late 1987 included only about 3,000 persons. The National Gay Rights Advocates' lawsuit was a symbol of frustration, and when FDA won a dismissal on procedural grounds, the frustration of activists deepened into cynicism.
O'Leary's concern with the FDA followed what now seems a natural progression in the AIDS epidemic's evolution of advocacy. Advocates initially aimed at speeding the discovery of the causal agent with a focus on the Center for Disease Control's funding in the 1981 to 1983 period. Then the advocates' concern shifted to the National Institutes of Health's limited research budget devoted to the search for the cause of AIDS. When American and French scientists identified the HIV virus, the advocacy goals then quickly shifted to funding for educating potentially affected persons about the methods of prevention. And they intensified their previous demands for science to discover therapies, cures, and preventive vaccines.

By the fall of 1986, the Surgeon General of the United States, Dr. C. Evert Koop, had issued and circulated nationally a 36-page report on the need for explicit public education on the methods of transmitting AIDS, in order to stop the exponential spread of AIDS. In addition, advocates of higher Federal AIDS spending, using a major study conducted by the National Academy of Sciences and released in October of 1986, focused on the need to increase Federal AIDS-related expenditures, again primarily those on research and education. The Academy noted that "The situation demands both immediate action to stem the spread of infection and a long-term national commitment to produce a vaccine and therapeutic drugs."

The political and budgetary response, criticized by some as too slow but defended by the chief national health
officials as appropriate, was to increase federal expenditures for AIDS-related research from $135 million in fiscal 1986 to a proposed $468 million in fiscal 1988 (a budget number that is actually set during the preceding calendar year, e.g., 1987.) A real increase in testing and education would occur with this new money.

Yet for the same fiscal 1986-1988 period, funding for the FDA's regulatory activities related to AIDS was slated to grow from only $10 million to $25 million. Unlike research and education, the role of drug testing and approval for new therapies was understaffed, underfunded and often misunderstood. While popular national publications like the *New York Times* and *NEWSWEEK* would report in 1988 the outcry of community activists over the slow pace of FDA drug approval activity, in early 1987 there were street demonstrations in San Francisco demanding access by AIDS and AIDS-Related-Complex ("ARC") patients to clinical trials testing experimental AIDS therapy drugs. The FDA was very much in the public spotlight -- without more funds and necessary reviewing scientists and physicians.

So it was quite natural that the gay activists in David Mixner's West Hollywood living room in May of 1987 were focused on bringing the state's chief law officer into a discussion about whether something couldn't be done in California to speed up trials of new drugs and to involve more AIDS patients in the testing process. Against this backdrop of criticism concerning the FDA, however, gay activists and others in the AIDS treatment
community in California were distressed and discouraged. California is characterized incorrectly as affected more than any other state by the AIDS epidemic, even though New York always has had more AIDS cases. AIDS was nonetheless at a desperate stage. These western activists felt stymied by the apparent reluctance of the Eastern-based Federal Government to be responsive to the health care needs of Californians.

The initial criticism of the Reagan Administration had focused on its slowness to respond tangibly to the AIDS crisis, particularly with research budget dollars. Only in Fiscal Year 1984 did the Federal government initially request AIDS-specific research funds from Congress. Yet Secretary of Health and Human Services Margaret Heckler's triumphant announcement in April of 1984 that the Federal government hoped to have an AIDS vaccine ready for testing "in about two years" created a climate of expectation that scientific reality just couldn't satisfy.

These activist Californians had followed closely the criticism of the Federal AIDS effort. Their experiences in their communities affirmed this criticism. The National Academy of Sciences' report entitled "Confronting AIDS" in 1986 and other sources, had provided confirmation on a national level of their opinions of AIDS research funding and particularly of their nascent but growing criticism of the ineffectual response of the FDA to the need to experiment quickly with possibly beneficial AIDS-related drugs. As clinical psychologist Rob Eichberg explained to Attorney General Van de Kamp, "So many people
diagnosed with AIDS and ARC are willing to be guinea pigs for these drugs. There just aren't enough [drugs] available for testing, so they're going to Mexico to get them or making home remedies."

Section 2.4 The Clash over Drug Testing and Licensing Philosophy

The philosophical issue underpinning the debate over AIDS-related drug testing and licensing had been thrust into national focus in the spring of 1987 by Larry Kramer, a founder of the nation's first and largest community self-help AIDS organization, the Gay Men's Health Crisis in New York City. Kramer is a widely acknowledged playwright, whose "The Normal Heart" exemplified the human nature of the AIDS epidemic. From the very beginning of the AIDS crisis, Kramer had distinguished himself by being a prescient critic of local, state and federal officials' unwillingness to engage the seriousness of AIDS as a disease.

In his acerbic yet telling style, in March of 1987 Kramer published in the New York Times (a newspaper he had once criticized for ignoring the AIDS crisis) a widely circulated and caustic critique of the FDA under the pointed headline of "The F.D.A.'s Callous Response to AIDS."

Kramer ridiculed FDA Commissioner Dr. Frank Young's widely heralded announcement on March 19, 1987, of an ostensible time-saving reduction in FDA drug approval rules. The FDA claimed that its new procedures could shave two to three years
off the typical seven to nine years required before drugs are released to general public use. Kramer noted that FDA's rules had been in circulation for years as draft proposals. Kramer also simply and poignantly pointed out that most currently diagnosed AIDS patients would die in significantly less time than the now-shortened FDA approval period.

Kramer also mounted his most fundamental assault on the scientific heart of the FDA regulatory process. Kramer argued that classic double-blind studies, in which some patients receive the test drug and others receive placebos, were not created with terminal illnesses in mind. Wasn't it inherently inhumane and cruel, Kramer suggested, for terminal patients willing to take experimental drugs to be denied that opportunity in the name of scientific concerns for toxic side effects? Was it fair for AIDS patients to participate in such double-blind studies, where half would by definition receive placebos in order to show subsequent refinements or discoveries in toxic side effects from the experimental drug? In its most graphic terms, Kramer's argument suggested that no toxic side-effect compared with AIDS now-certain outcome -- death. Where experimental drugs have passed muster in Phase I safety/toxicity trials (discussed in Chapter 11 below), Kramer argued that such drugs should be permitted for individual physician use and community tests as well as in more formal clinical trials as an exercise of "compassionate usage." Such uses were an acknowledged and historical practice, but heretofore FDA had not encouraged their use in the AIDS crisis.
Kramer's essay was published only a week after the FDA's approval of AZT, the first AIDS therapeutic drug licensed by FDA. AZT was constantly touted thereafter as visible proof of the efficacy of FDA's regulatory approaches announced in March, 1987. In short order, FDA also announced on May 22, 1987, new "compassionate care" rules under which certain AIDS patients could use novel drugs after a limited period of effectiveness testing, even though their toxicity side effects were undetermined pending further clinical trials.

Section 2.5 - The California AIDS Drug Testing Innovation

In the early summer of 1987, the focus of the AIDS epidemic in California and the nation was shifting rapidly to AIDS drug testing and licensing. It was not surprising then that California's Attorney General moved quickly after his emotionally draining conversation in West Hollywood to try to change national policy on California's top priority -- AIDS drug testing and licensing. As Van de Kamp recalled, "The one thing I came away with was a resolve to test [AIDS drugs] independently in California," explaining that while he wasn't sure if such a plan could legally be done, he nonetheless would pursue it because "it might make some sense, given the size of the [AIDS] problem in California. The bottom line conclusion is a human one."

A clear policy agenda was enunciated amidst the poignancy of the West Hollywood meeting. Couldn't California speed up trials of new drugs and involve more AIDS patients in
the testing process? Could California start an AIDS-related drug testing and licensing program of its own?

Van de Kamp on the very next day after his West Hollywood meeting began an Attorney General's Office initiative to draft policies and legislation if necessary to test AIDS drugs in the state, placing this issue as a top priority over any other issue in his office.

Section 2.6 California's Existing Sherman Food and Drug Act

When John Van de Kamp asked Special Assistant Attorney Richard Jacobs to spearhead his research on a legislative initiative to allow California to test AIDS drugs independently of the FDA, Jacobs lost little time. By May 20, two days after the West Hollywood meeting, Jacobs developed the first Attorney General white paper on the issue. Yet Jacobs was surprised to learn in his research that California has always had the power to test and even license drugs independently of the FDA.

Under the state's Sherman Food and Drug Act ("Sherman Act"), California since 1939 has asserted its independent right to test and license drugs for public use within California state borders. In 1938, Congress adopted a Federal law for interstate "new drug" products and it did not discourage states like California from adopting their own parallel laws. That is why California's Sherman Act had been modeled upon the Federal requirements originally incorporated into the Federal law in 1938. This California statute was amended from time to time to
conform to Federal FDA requirements (including mandating that a New Drug Application ("NDA") under California law contain the exact same categories of information as that required by Federal law), but California retained its own independent law basis for approving and disapproving of such NDAs within California.

California state law didn't clash with FDA's national approval system. California state law provided a complete exemption for any new drug for which Federal FDA granted an Investigative New Drug ("IND") status based upon laboratory data (a concept discussed below in Chapter 9). If the proposed drug moved to New Drug Application status and ultimate approval by the FDA, California similarly provided a complete exemption from further state regulation of the proposed drug.

While this policy precluded unnecessary state regulation in the face of Federal approval, this approach also left dormant California's independent drug testing and licensing powers. Thus, in 1987, the Special Assistant Attorney General Jacobs quickly realized that California's Sherman Food and Drug Law did not have to be changed to accomplish the goal of testing AIDS-related drugs in California. Rather, California merely needed to activate and modernize its long dormant policy of independently controlling in-state programs of drug testing.
Section 2.7 The Van de Kamp Proposal

On May 21, 1987, three days after the West Hollywood meeting, Attorney General Van de Kamp went public with his AIDS drug testing proposal in a speech to a leading gay activist organization in California -- the Harvey Milk Democratic Club. [Footnote: This political club was named for the nation's first avowedly gay elected official who was subsequently assassinated in 1977 along with San Francisco's Mayor George Moscone by a mentally distraught former San Francisco supervisor and political foe, Dan White.]

In his speech Van de Kamp discussed his West Hollywood meeting and criticized the FDA for what he called its three speeds of action: "slow, slower and glacial." Noting that 70% of the drugs eventually approved for use in the United States by the FDA are on the market in other countries long before Americans can buy them, Van de Kamp argued that the length and expense of the FDA process for drug testing and licensing favored only the biggest and best funded drug companies. Blending his compassionate view of AIDS victims with a novel appeal for small business, Van de Kamp argued that the barriers to small companies are nowhere "more formidable" than at the FDA. Van de Kamp suggested further that promises of California's home grown biotechnology revolution would be unrealized in the AIDS field unless fundamental changes occurred in national drug policy.

Van de Kamp stated the challenge starkly: "[If necessary] we should take responsibility for testing and
approving AIDS drugs out of the hands of the FDA." Calling upon California, in light of its enormous economy, innovative businesses and near legendary university system to resist "passively awaiting the pleasure of the FDA," Van de Kamp suggested that California should move on its own to help its AIDS victims by forming "a joint private-public-academic consortium to serve as the link between research, testing and patient care."

Recognizing the controversial nature of his proposal, Van de Kamp cautioned that "our aim would not be to duplicate or replace the federal process. Manufacturers who won state approval could only test and sell their drugs in California."

But Van de Kamp premised his proposal on unleashing the creative power of smaller companies to escape the FDA "mire." These companies could work with California's AIDS patients and clinicians to advance AIDS-related drug testing beyond the limited FDA efforts to date.

Anticipating future criticism, Van de Kamp also announced creation within his office of a Task Force on AIDS Consumer Fraud, to investigate and prosecute fraudulent and worthless AIDS cures that were constantly hyped within the vast California underground press and by numerous small stores within the gay and natural health food communities.

The die was cast -- the challenge was made. Van de Kamp had squared off with the AIDS medical establishment, the FDA and even California's Governor. The results became a textbook case in political change.
Section 2.8 The Debate over the Van de Kamp Proposal

Following extensive discussions with the scientific research, business and legal experts, Van de Kamp held a major meeting on June 17, 1987, to review with medical and business leaders his proposal. This meeting addressed the spectrum of concerns about California "going it alone," including the potential for decreased scientific scrutiny over research and for excessive business claims of success for investors. They also discussed whether a California-only market would be large enough to sustain scientifically adequate research under California-only research protocols.

This meeting underscored the potential interest of California-based research and development firms. With at least four of the nation's largest independent biotechnology companies headquartered in California, the potential medical, scientific and academic talent pool was in place. Yet with the cost of developing a new drug therapy running around $20 million and a vaccine $50 million in 1987 dollars (see Chapter 16), financial commitments to AIDS-related drug research had to be massive. Would California's independent AIDS drug testing initiative flounder due to lack of manufacturers' interest in a single-state market?

The quick answer was no. When Jonas Salk, who developed the first successful vaccine against polio, indicated that his new company, Immune Response Corporation of La Jolla, California, would utilize a California-based testing program in
Treatment Review Committee that would review new drug applications for AIDS-related drugs and recommend approval or denial to the Director of California's Department of Health Services ("CDHS"), the agency charged with enforcing California's Sherman Food and Drug Act. This committee would also assist the CDHS in developing data submission formats and protocols for the clinical testing of AIDS-related investigational new drugs. Finally, the committee would either develop or review proposed protocols for the selection and enrolling of patients in clinical trials of AIDS-related drugs, and also review potential treatment centers and/or clinical physicians who might also manage AIDS-related drug testing. Jacobs also proposed a financial aid program of loans and grants for the development and testing of AIDS-related drugs by California manufacturers.

Over the next six weeks, the debate over the latest Van de Kamp iteration of a California-based "fresh start" (as its admirers dubbed Van de Kamp's ideas) sharpened. The FDA subtly opposed the proposal, primarily by questioning the reliability and safety of California-supervised research, implying that California's efforts would resemble Nevada's earlier attempts to legalize Laetrile as a cancer cure. FDA also promoted its "soon to be announced" changes in procedures that would be responsive to California's concerns. Local physicians responsible for AIDS policy, such as Dr. Neil Schram (former Chairman of the Los Angeles City-County AIDS Task Force) and Dr. Martin Finn, medical director of the AIDS program for the Los Angeles County
Department of Health Services, emphasized that California's efforts could not be to the exclusion of other nationwide efforts. The FDA and certain drug companies downplayed the ability of California to replicate FDA's process that winnows out unsafe and ineffective substances.

But editorial opinion, especially in the Los Angeles Times began to underscore the unease with which the public viewed the traditional caution in medical research when it came to the subject of AIDS (an illustrative editorial entitled "Foot-Dragging on AIDS" ran on July 28, 1987).

And then on August 12, 1987, the General Accounting Office reported to Congress that local health officials and nationally recognized experts were expressing frustration with Federal AIDS efforts, including those that appeared to inhibit rather than promote AIDS-related drug testing. This report served to document California's frustration.

In light of an apparent behind-the-scenes California political consensus set against this new national critique of the FDA, Richard Jaccob finalized his recommendations for legislation to Van de Kamp on August 15, 1987, and discussions began immediately to find an appropriate bill in the waning days of the California legislative session, in that legislators were expecting to adjourn for the fall elections by the middle of September.
Van de Kamp drafted legislation to incorporate Richard Jacobs' approach to a bill that was ultimately carried by the California Legislature's only physician, William Filante. Assemblyman Filante represented Marin County, long satirized for its hot-tubs and health food fads. Yet the politics of this alliance were interesting, in that Van de Kamp is a Democrat and Filante is a Republican. Filante's legislation was originally introduced to deal with an esoteric medical issue concerning tissue typing and regulation. But in a tradition long recognized in California's unique legislative process, Filante allowed his bill to be "highjacked" and "gutted" to incorporate Van de Kamp's AIDS initiative.

The Van de Kamp/Filante legislation incorporated Richard Jacobs' concept of promoting testing and even licensing of AIDS-related drug products within the existing framework of California's Sherman Food and Drug Act. The bill did not adopt any different standards or methods of drug evaluation, and it retained California's requirements that parallel the FDA's safety and efficacy demonstration requirements for any new drug. But the Van de Kamp/Filante legislation nonetheless made it legally clear that AIDS-related drugs could be tested and licensed in California, separate and apart from the FDA approval system, and that California health care officials would expedite any bureaucratic requirement to ensure the most rapid evaluation and action on AIDS-related drug proposals. In terms of AIDS, the
sixth largest economy in the world was also the second largest U.S. jurisdiction in terms of AIDS-related cases. Thus, the bill's proponents asserted, California would be an attractive venue in which to test and license drugs, even if interstate commercial distribution would require subsequent FDA approval. Indeed, the unspoken consensus view was that once licensed in California, a drug's approval by FDA would in all likelihood become irresistible.

On August 31, 1987, Assemblyman Filante announced at a press conference in Sacramento his introduction of the Van de Kamp initiative in its final form as Assembly Bill 1952. Incongruously flanked by conservative Republicans, including John Doolittle, who had consistently led the fight for draconian AIDS legislation, and liberal Democrats like John Vaconcellos, author of the legislation establishing the famous California Commission on Self-Esteem, Assemblyman Filante basked in this unusual glow of bipartisan support. Filante declared that "Whatever is possible should be done, and it isn't. We have the authority here in California to do our own testing under our own protocols." Promising to follow but not to be held to FDA guidelines, Filante emphasized that "The FDA is not meeting the needs of the people of California."

Joining Filante as well at the press conference, Van de Kamp sounded a sterner theme. "There are two places where this will echo like a thunderbolt. One is the corridors of the
federal medical bureaucracy, and the other is in the hearts of AIDS victims everywhere."

Section 2.11 The Opposition to Van de Kamp's Proposal

However, Filante and Van de Kamp were not unopposed in their AIDS-drug testing initiative. Rushing to emphasize that the bill wasn't necessary, state health officials conceded that they were already supervising the testing of at least a dozen experimental drugs, including two monoclonal antibodies used in cancer research and 10 radio-pharmaceuticals used in X-ray diagnoses.

A number of physicians active in the AIDS treatment community, including the former chairman of the Los Angeles City/County AIDS task force, the medical director of the AIDS Program for the Los Angeles County Department of Health Services, and the medical director of the AIDS Task Force in San Francisco, objected to Van de Kamp's approach on the grounds that California-based research would be less scientifically exacting than FDA-sanctioned testing. Their fears focused on the localized nature of research confined to one state, though the testing of AIDS drugs had historically utilized California as a critical testing environment.

Weighing in against the bill, the San Francisco Examiner's editorial page reflected these views, suggesting that California had neither the state bureaucracy nor the scientific process to embark upon an AIDS-related drug testing program. The
Examiner emphasized the rapidity of AZT's approval by FDA, and darkly hinted that the poor clinical showing by another contemporary AIDS-therapeutic aspirant, dideoxyctidine ("DDC"), confirmed that historical FDA methodology should not be bypassed. "This theory (of California's independent action) is fueled by false hopes," the Examiner concluded.

The California medical AIDS establishment also began to organize in opposition to the Van de Kamp/Filante legislation. The opposition of Dr. Paul Volberding, a near legendary AIDS clinician who played a prominent role in raising both medical and social attention to AIDS, figured prominently in this medical groundswell of opposition. While Volberding was criticized on the grounds that his now-healthy research funding from the National Institute of Health made him too beholden to the federal government to be objective (a cruel charge in the face of his years trying to obtain just such appropriate federal research funds for AIDS studies in San Francisco), his opposition figured prominently in the fears of many in the medical/research community in California that the politicians were getting a bit ahead of a proper research system.

However, the key misunderstanding concerning the legislation was an incorrect assumption that the State of California would somehow actually conduct the research. Businesses lobbying in support of the legislation, including ICN Pharmaceuticals, the developer of the promising but controversial AIDS therapeutic drug ribavirin, insisted that the private sector
would, as under the FDA, in fact need only state government approval to test AIDS-related drugs, not state research funds to conduct the research. Certain California businesses, including Syntex, California's largest drug manufacturer, and Cetus, a pioneering biotechnology company, were less enthusiastic, fearing perhaps that the FDA would look disapprovingly upon companies utilizing the California AIDS-related drug testing option and retaliate against those companies' other products in the FDA approval pipeline.

However, the editorial page of the Sacramento Bee on September 8, 1987, seemed to capture the popular mood. After approvingly reviewing the criticisms of the FDA's approach to AIDS drug testing and commending California's innovative spirit, the Bee emphasized that "there remains a risk that a combination of pressures from desperate AIDS sufferers and eager drug companies will weigh more heavily than scientific evidence." This philosophy could be extended to research on Alzheimer's disease and heart ailments as well, where the risk of toxic side effects was perhaps more problematic than with death-dealing AIDS. The Bee concluded, however, that: "On balance, it's [Van de Kamp's idea] worth a try."
Section 2.12 The Legislature's Actions

In the legislative arena, however, the decision of both houses in the State Legislature was quick and decisive. Acting in less than ten days, the State Senate approved Filante's bill on a 38-0 vote. Brue Decker, Chairman of the California AIDS Advisory Commission, exulted that "The Legislature is no longer simply trying to put a Band-Aid on AIDS problems. It is a very clear indication that the Legislature is taking a long-term, thoughtful, serious approach to AIDS." Senator Doolittle, in the floor debate, ironically emphasized his support as a conservative, noting that "I think this is an essential bill to do something to help people who suffer with AIDS and who, as a result of the slowness of the FDA to approve new drugs are being driven to other countries to seek treatment there."

The next day the Assembly followed suit, approving Filante's bill without amendment on a 76-0 vote. The Assembly was hushed as Assemblyman Eric Seastrand rose in support of the bill, for while Seastrand was another conservative legislator, he had only recently been notified of a recurrence of cancer of the colon.

"Someday and one day perhaps you will have the opportunity to confront something that is as deadly as cancer or perhaps AIDS, and I can tell at that point that when it's your life, you are going to use what you think is the best, even if all the scientists in America, if all of the people with the Ph.D.'s and medical doctorates, perhaps disapprove. I ask for an
aye vote on this bill, and I'll tell you it doesn't go far enough." Applauding Seastrand's populist, moving testimony, California's legislators clearly favored an independent approach to that of the FDA. However, the debate was clear that while California might adopt alternative procedures, the scientific rigor of review and demonstrated safety would not be compromised.

Section 2.13 The Feinstein Opposition

Nonetheless, San Francisco's Mayor Dianne Feinstein strongly urged California's Governor George Deukmejian to veto the Van de Kamp/Filante legislation. Acting at the request of her local health officials, Mayor Feinstein argued again that California was imprudent in an action that might reduce the scientific standards by which to evaluate drug efficacy and safety. In writing the Governor to urge his veto of Filante's bill, Feinstein stated her stark view that "I believe these (testing and drug approval functions) belong solely to the FDA."

Feinstein led the last medical establishment charge against AB 1952, backed by Dr. Volberding's statement that "the way to speed the process of curing AIDS isn't to create less sophisticated (testing) systems just because we feel a sense of urgency. As much as we feel that, we need to stay rational and not make drugs available that are harmful.

However, the AIDS medical establishment was not monolithic. Another prominent AIDS dermatology clinician in San Francisco, Dr. Marcus Conant, was among the first physicians in
1981 to recognize that an epidemic was taking place in both New York City and San Francisco. Dr. Conant, now chairman of the California Department of Health Services' AIDS Task Force, argued forcefully that his personal study of the FDA system convinced him of the need of the Van de Kamp/Filante legislation. Objecting to Volderbing's characterization of potentially less scientific reviews in California, Conant argued that "The agency (CDHS) is committed to taking a deliberate path to prevent a mistake."

Section 2.14 Governor Deukmejian's View

In the last instance, the Republican Governor George Deukmejian signed the legislation, but indicated that he did not plan to allow California to part company with the FDA. "I am concerned that by signing this bill into law, the public will expect California, independent of the FDA, to approve drugs for use in the treatment of AIDS. Quite the contrary is true," the Governor noted in his message of approval on the bill. "The United States Food and Drug Administration is making the approval of AIDS-related drugs a priority...The review and approval of drugs is a national issue and it is unrealistic to expect California to duplicate their work or resources...We should not, though, unrealistically view this legislation as a substitute for FDA approval of drugs in the treatment of AIDS or as a precedent for drugs in the treatment of any other disease."
While calling for FDA/California cooperation, the Governor nonetheless signed the legislation, allocating $500,000 to enable California to proceed with its now reaffirmed legal authority to "review and approve for use in California AIDS-related drugs."

Section 2.15 The Post-Approval Perspective

The FDA was quick to object, albeit obliquely, with a California-based spokesman observing dryly that "The state does not have a complete understanding of what's involved. The review of drugs is a very complicated system that does not have a great deal of margin for error. For the state to be in a position to gear up to do that, they will have to confer with us extensively. It's very difficult to produce any kind of drug that is not subject to Federal regulation."

Nonetheless, the Washington Post trumpeted Van de Kamp's applause for Governor Deukmejian's action. "The State of California is in the business of testing drugs that hold promise for curing or treating AIDS...(the Governor's approval) is a clear statement that, in the midst of a killer epidemic, business as usual in the drug-testing process just isn't good enough. Whether we like it or not, California is in the forefront of this struggle. We are on the front line taking casualties; and we must be in the front ranks of research and testing. California will be the first state in the nation to engage in this effort."
Van de Kamp's view was echoed by Dr. Marcus Conant, who also applauded Deukmejian's approval of the Filante bill by noting that "This is a bold experiment that I hope will prove fruitful." He suggested that the state hoped to work with companies "in partnership, helping them out, rather than in the adverserial way used by the FDA."

Dr. Kenneth Kizer, the Director of the CDHS and the man ultimately authorized to approve AIDS-related drugs for testing and licensing under this new bill, was more cautious. Kizer was uncertain whether testing under state auspices in California would move faster than testing conducted under FDA auspices, and he said it remained to be seen whether it would be advantageous for companies to test drugs in California in addition to conducting FDA-approved tests.

Observers noted that while there was a danger that California's procedures might not meet FDA's standards, thereby thwarting national distribution, the real challenge lay in dramatically increasing the number of patients participating in AIDS-related clinical drug trials.

The commitment of Dr. Stuart Richardson, the head of CDHS' Food and Drug Section mirrored the Governor's concern for cooperation with the FDA. Dr. Richardson would work closely with, and in a similar fashion, to FDA's drug review staff.

The key question would now be tested. Would anyone use the new California process?
Section 2.16 California's Challenge to FDA

In a near textbook case of throwing down the policy and political gauntlet, California's John Van de Kamp and Bill Filante had teamed up to call the FDA bluff. Would FDA oppose California, ignore California, or confront Larry Kramer's philosophical challenge and make internal changes in traditional procedures? Could scientific methods adjust to unique epidemics like AIDS without sacrificing thoughtful and necessary public health protection?

The applications quickly began to arrive on Dr. Richardson's desk. The die was cast.

Administered by the Food and Drug Division of the California Department of Health Services ("DHS"), the California AIDS-testing legislation took effect in January of 1988. During the first year of operation, 14 applications for various types of AIDS-related drugs have been received.

Eight of these applications have received vigorous review, resulting in only three applications being approved to go forward to Phase 1 testing. However, these approvals include the vaccine development effort of Dr. Jonas Salk at the University of Southern California.

We shall return to review the actual process and functioning of the California legislation in later chapters, after we have reviewed the FDA process in detail.

California's so-called "fresh start" initiative, as the Van de Kamp/Filante legislation was dubbed, indicates the far-
reaching nature of the AIDS epidemic. Openness to change is essential. Unnecessary controls deserve re-examination. Serious policy and even legislative change can be anticipated. The goal is to cut away any retarding or inhibiting requirements that are not soundly linked to scientific and legal mandates.

We turn now from the general discussion of how AIDS-related drugs are handled by science and government to discuss the actual regulatory apparatus of the FDA and California.
CHAPTER 3

THE RESPONSE TO AIDS: REGULATORY EVOLUTION, NOT REVOLUTION

"Those who fail to learn from history are condemned to repeat it", said the historian Santayana, and he may have been addressing America's response to the epidemic of Acquired Immune Disease Syndrome (AIDS).

The modern epidemics have all been marked by three phases of government response:

* detective work, stumbling at blind alleys and later gearing up for the road to critical discoveries;

* problem-solving work within the government, chronically underfunded and run by a few very dedicated scientists; and

* regulation of the solutions, mediating the private industry's quest for financially rewarding remedies by control of the epidemic-solving "pipeline" of drug development.

Polio, tuberculosis, syphilis, yellow fever, and even swine flu have gone through these cycles. The distinction which AIDS has experienced is its fatal effects on generally healthy people; its rapid and insidious spread through contact of bodily fluids; and the complexity of its molecular structure and activity. But the governmental involvement with this epidemic
follows a familiar pattern. AIDS has experienced an evolutionary rather than revolutionary spread.

**Detective Work**

The Centers for Disease Control is the nation's "disease detective" agency. It studies epidemiology (patterns of disease causation) and microbiological factors in disease spread.

Evolution has loaded the first stage of government response to AIDS - the stage of CDC work - with new survey tools, high speed computers, telecommunications and laboratory equipment which the healing sciences could only dream about during past decades. The disease detectives come armed with amazing capacities to discover the subparticles of matter within cells, and to analyze and differentiate extremely small fragments of clues. Their proud discoveries of the reasons for illness today rank the Center for Disease Control as the top disease-hunting team in the world.

CDC tracks down the patterns of disease, correlates and computes potential causes and drives its network of researchers toward the clues which enable them to break the secrets of the offending germ or virus. Its end product is sometimes slow to arrive but its record of accuracy on final judgments is strong.

**Problem-Solving**

Evolution has also been very important to the National Institutes of Health ("NIH"), the heart of the nation's problem-solving apparatus for basic medical research needs. Through its
twelve major research Institutes the NIH has funded much of the basic research which supports studies of heart disease, cancer, AIDS, diabetes, and a host of other diseases. When a new challenge to the medical system is presented in the form of a new disease, NIH and its grant program scientists at laboratories around the country become involved in the basic problem-solving tasks.

Evolution in solving medical research puzzles is expensive. NIH funding for all diseases has been good, but until recently NIH appropriations for AIDS had not kept pace with the costs of medical research. The costs of new state-of-the-art equipment, clinical programs for patient care and examination, and other costs of medical experimentation are rising faster than the Administration has sough funds, even in the face of a Congressional willingness to allocate them. But NIH has been a key player in basic research, evolving into a crucial player in every contest against new killer diseases.

Relation of Possible Solutions

Evolution has come most slowly at the third stage of government - the regulatory stage. Regulation occurs when solutions are offered to a problem which has been identified and tracked. The Food and Drug Administration's reputation is sterling, but its actual body of key regulators is a handful. FDA medical officers who review drugs before approval are no more than 175 individual physicians, perhaps 50 at most working on
AIDS-related products, and with hundreds of scientific and support personnel assigned to drug regulatory activities. But evolution will be inherently slower at this phase because of two critical policy choices made by Congress. The pace of evolution for FDA cannot be seen outside of this congressional context.

The Congressional Choices

What does Congress decide and how does it affect the evolution of AIDS? Its decisions impact on the process of developing drugs, and the criteria for allowing them to be used on people.

The first major policy choice is that the private sector controls the drug development "pipeline". Basic research into potentially useful compounds begins with private sector pharmaceutical chemists more frequently than it does with NIH scientists, and the novel work of academic researchers into pharmaceutical molecules is more frequently funded by industrial grants than by NIH.

Congress chose this pipeline status by not choosing a heavier investment in "applied research" and drug development. The pipeline for AIDS drugs is as much a part of the free enterprise market economy as the search for a better coffee mug or a better light beer. It is a policy choice rarely questioned today. Apart from some vaccine work, government's role does not extend into development of the actual drugs to be used for each
major disease. Here, as in the California laws discussed above, the private sector does the research to fill the pipeline, while public sector agencies regulate the end-of-pipeline new product sales.

Would the pipeline work better in government's hands? An alternative of fully government-financed research in lieu of the profit incentive of the private sector would probably fail to attract the experienced senior researchers whose intuitive skills hasten the discovery of effective compounds. The costs to Congress of trying to replicate private scientists' dozens of labs would be nothing compared to the costs of attracting and sustaining the best research minds to a standardized federal salary scale with no stock options, no bonuses and limited patent rewards. People-costs in pharmaceutical research have been evolving, too, evolving upward with the demand for limited numbers of expert Ph.D. and M.D. researchers.

So the policy decision exists. The pipeline is private. Once a serious commitment for drug development occurs it will occur with private funds and private sector incentives. If the private sector has no products to review, no magic bullets to offer, then all the approval criteria among the world's regulators are useless.

The second Congressional choice affects the criteria for allowing drugs to be given to people. Congress gave the FDA power as "gatekeeper" for drugs, and its instructions were set firmly at a level which excludes many products. Congress opted
for greater certainty that the few drugs which reach the market will actually work (and work to an extent sufficient to justify their inevitable risks).

Congress might choose to let more drugs on the market. It could drop the legal requirement, first established in 1963, that more than one full-scale comparison study be done between the test product and a less effective product. Congress could set up a channel of approval which is less demanding for AIDS drugs, for example, and let more of the pipeline drugs onto the market. Congress could definitely allow any AIDS test to proceed, just as the Florida legislature several years ago named a select few cancer drugs which the state allowed to be sold there, despite doubts of their effectiveness.

Congress could do this, but it hasn't. The political debate rages on -- should the standards change? Is the pipeline too difficult? Are drug breakthroughs for AIDS discouraged? If the answer were easy, Congress would have evolved into a change, but it is not easy and no change is on the horizon today.

Where's The Next Evolutionary Milestone?

Any chronology of evolution looks for remarkable breakthroughs. The establishment of a CDC hypothesis about the causation of AIDS by the human immunodeficiency virus (HIV) was a milestone. The development of proof that AIDS was a disease communicated by the passage of bodily fluids infected with the HIV virus was another milestone. The findings of French
scientists and American NIH scientists about the actual HIV molecule were a milestone of microbiological problem solving. Milestones mark time points; they do not speed up their occurrence.

Each of these milestones are accompanied by public attention and public criticism of some aspects of the agency's work. CDC received criticism from some quarters for its inability to pin down the complexities of the HIV virus and its transmission factors. NIH received criticism for the appearance of a slow response to the need for HIV information from which a cure would be developed. The Executive Branch as budget proposer and the Congress as the source of funds and priorities got even more criticism for their perceived lack of attentiveness to the urgency of the AIDS mission.

The momentum for evolutionary change in AIDS detective work and problem solving came in part from science and in part from the response to these critical reviews. Persons with serious illness should be optimists; Americans relish a good fight with a hopeless disease like polio, tuberculosis, or cancer. Our society encourages hope and our mass communications media splash the telethons of disease-fighting progress for all to view. The momentum for the attack on AIDS existed in 1982-1983 at CDC, in 1983-1984 at NIH and continues on to this day at each of those federal agencies.

The next milestone is a regulatory one -- the positive improvement of the Food and Drug Administration's system so that
it will not only avoid the problem of halting the flow from the pipeline, but will also pump new technologies through the development pipeline by positive encouragement.

The Momentum for FDA Activity on AIDS

The momentum for FDA to change the regulatory system, as to encourage development of successful AIDS drugs, has taken longer to develop than did the momentum for change at the other stages. The momentum of political direction from Congress came first through hearings on AIDS disease progress. Advocacy groups began to meet with FDA more frequently; CDC and NIH shared ideas and insights; drug developers went to FDA with NIH is active support; and FDA operating level people concerned with viral illnesses became very interested in the encouragement of AIDS products.

Change almost always requires forceful leadership. The priority-changing forces which oversee FDA -- the Congressional appropriations subcommittee and the Department of Health & Human Services -- directed more FDA action and promised more funding for greater FDA resources in 1986-87. A superb effort was made to recruit and promote the infrastructure of people needed to concentrate on AIDS drug products at FDA. And Commissioner Frank Young's very committed leadership team at FDA gave its personal attention to the outsiders' challenge.

Criticism of FDA was relatively slow to develop, compared to the prior track record of AIDS organizations'
critiques of NIH, which has tangible molecules and virus findings to show as its "products," and CDC, which experiences the cycles of admiration and criticism which all detectives must expect. The FDA has no similar victories of its own making. It responds to private product developments. In its drug approval history, FDA people have succeeded by non-approval, as witnessed by the dozens of Congressional hearings attacking certain products' approval by FDA and not one hearing praising the medical officers who worked to approve a drug.

Any large organization, whether an army, navy or bureaucracy, draws its living lessons from its history and its rewards structure. Congress praised FDA reviewers' resistance to drug industry pressure for approval. President Kennedy awarded the Medal of Freedom to the FDA reviewer who refused to approve a drug later found to cause birth defects. Drugs with side effects much less serious than those of AZT, the first AIDS drug, have been removed from the market for excessive risk. So the critics of AIDS drug conservatism understandably had a tough time making many points against the FDA.

For example, FDA's AIDS critics demanded broader availability of investigational drugs; FDA moved slowly to alter its testing rules, because of the cumbersome process of changing its complex rules and the even more difficult task of adjusting and balancing these rules for the critical AIDS cases without allowing abuses for the many lesser drugs which are much more frequently the subject of tests.
The critics offered the challenge that FDA was too demanding and thus inhibited new pharmaceutical entities from being marketed. FDA replied that all drugs carry some risk; that demanding proof of a drug's effectiveness was the policy chosen by Congress and endorsed by most physicians, to balance real benefits against those real risks; and that FDA did not control the "pipeline" and could only approve products whose private developers really were ready for approval.

So Why Did FDA Change?

A historian of science like Thomas Kuhn might say that FDA changed because the critical mass of scientific need for change caused the paradigm of consensus to change. The cynics would focus on Congressional demands and funding for change, while the humanists would document that the severity of the costs of AIDS all came together at the right juncture to change FDA.

An observer of organizational behavior will say that conditions within a bureaucracy must be ripe, no matter how much the external pressure, before change can really occur.

The critics today will still say that not much has changed, that FDA still does not control the "raw material" of compounds which FDA can process through its approval pipeline, and that even if the institution controlled its workload, the individual reviewers are governed by their legislative limits and by the incentives which still demand too much caution.
The key to this conversion is to understand the evolution of policy, especially scientific policy. Sometimes everything matters, and perhaps all at once, before the inevitable change occurs in a manner that with hindsight should have seemed foretold by events. Hindsight concerning AIDS is extremely unreliable. People may charge that politics, ambition, permissiveness, fundamentalism, or fears like homophobia individually or collectively explain how all the players in the AIDS policy drama have acted. While this book offers facts for reference, we frankly admit that the "why" questions of policy AIDS change remain to be answered.

We turn now to our more basic purpose in writing this book -- to discuss the "how" and "what" questions of the FDA changes in drug regulation policy today.
CHAPTER 4

A SCIENTIFIC
INTRODUCTION TO AIDS

Section 4.1 - Overview

This chapter attempts a brief explanation of the science of AIDS. While the reader conversant with genetic microbiology may find it simple, we acknowledge that the burdens of translation have not been easy. Other periodicals and books which give more simple explanations may be obtained for a less detailed but perhaps more simplistic approach.

The Acquired Immune Deficiency Syndrome ("AIDS") results from infection with the Human Immunodeficiency Virus ("HIV"). The disease AIDS usually develops several years after the initial infection. For much of that interval, the infected person remains without visible symptoms and apparently in good health, but nevertheless can spread the HIV infection to those who contact his blood or sexual fluids.

It is this period of invisibility which makes early detection and mitigation so difficult. This prolonged latency, during which neither the victim nor his sexual partners may suspect that infection has occurred, is an insidious characteristic of HIV which has contributed to its rapid spread. The latency period of HIV, its selective ravaging of the immune
and nervous systems, and its ability to evade protective vaccine
are properties of this virus which make it especially fearsome to
its victims and a unique challenge to the public health system.
The origin of these properties can best be understood in terms of
the molecular biology of the virus.

Section 4.2 - Molecular Biology of HIV Infection

It is useful to preface the search for the AIDS drug
with the explanation of what researchers know about the tiny
(e.g., are too small to be seen under a normal microscope)
molecules which are responsible for this illness. Like other
viruses, HIV is an extremely simple organism, comprising only a
couple proteins surrounding a small amount of genetic material. The
outer coat of the virus is composed of many molecules of a single
type of protein, a glycoprotein of molecular weight 120,000,
known as gp120. Immediately underneath the gp120 is a thin
membrane-like layer of fatty material. The membrane is traversed
by a protein of molecular weight 40,000 (p40). Both p40 and gp120
are derived from a 160,000 precursor protein by a simple
enzymatic cleavage. Inside the membrane is a short stretch of
genetic material which contains all of the hereditary information
necessary to make more virus particles. Also within the membrane
layer are two enzymes which are indispensable for replication of
the virus. One enzyme is an "endonuclease," which makes cuts in
the genetic material of the host cell infected by HIV. The
second enzyme is a "reverse transcriptase," which converts the
genetic material ribonucleic acid ("RNA") into deoxyribonucleic acid ("DNA").

Although most living things encode their genetic information in DNA molecules, HIV genes are coded by the related molecule RNA. After HIV infects a cell, it inserts its own genes into the genetic material (the "genome") of its host. To accomplish this result, the reverse transcriptase enzyme of the virus makes a DNA copy of the RNA genes of the virus. Then the endonuclease enzyme cuts open the host chromosome and splices in the DNA form of the viral genes. In this way, the infected host cell is made to carry the viral genes in a form which cannot be detected by the host's immune system, until such time as the viral genes are activated and begin to make more virus particles.

The molecular structure of the HIV envelope protein gp120 apparently determines which cells of the human body will be infected, and consequently the symptoms of the disease. A short region of gp120 has the ability to bind tightly to a "receptor" molecule found on the surface of certain kinds of lymphocytes. Lymphocytes are the cells which mount the body's immune response, and therefore are indispensable in controlling infections. The type of lymphocyte to which HIV binds is known as the T-helper cell, so called because of its role in activating other lymphocytes to fight a particular infectious organism. Without this T-helper activation, the other cells of the immune system do not respond properly.
After binding to the T-helper cells, HIV particles may be taken up by the cell and infect it. When the viral genes are activated, the cell produces a large number of new viral particles which are released when the cell ruptures and which subsequently infect more T-helper cells. The HIV particles also kill T-helper cells by another mechanism: since each virus particle has numerous gp120 molecules on its surface, it can bind several T-helper cells together. Large complexes of many cells cross-linked by a viral "glue" can form. The cells eventually fuse to form a "syncytium" or giant multinuclear cell, which is nonfunctional and quickly dies. The net effect of these and perhaps other mechanisms is a profound loss of T-helper cells, and a consequent loss of immune system function. The weakened immune system loses its power to defend the body. The infected person then falls victim to a wide variety of secondary infections which define the disease AIDS.

The binding region on the gp120 envelope also explains one other prominent feature of AIDS, the dementia which frequently occurs. Some nerve cells in the brain possess the same molecule found on the surface of T-helper cells. These neurons also may be infected, resulting in a progressively worsening confused state in which loss of short-term memory and decreased attention span are commonly observed.

In recent days, at least two other strains of the HIV virus have been identified. Dubbed HIV-2 in mid-1988 by its initial discovery team from the University of California at San Francisco.
Francisco ("UCSF") and from Abidjan, Africa, the first HIV-2 isolate was confirmed in late 1988 by another team at UCSF. However, the later discovery came with dark implications, in that for the first time both the HIV-1 and HIV-2 viruses were isolated in the same individual, a female Ivory Coast patient, demonstrating for the first time that both viruses can infect the same individual. This particular HIV-2 isolate also appears, unlike the earlier HIV-2 isolate, to be a potent cell killer. This study also confirmed that infected individuals can have antibodies to both HIV-1 and HIV-2.

Section 4.3 - Chronological Review of AIDS Research

Scientific research focused primarily upon cancer led to the early scientific breakthroughs that powered the AIDS scientific scramble of research and development in the 1980's. Scientists first discovered that RNA tumor viruses replicate via a retrovirus DNA intermediate, a critical discovery paralleled by that of reverse transcriptase in the early 1970's. With the documentation of proviral DNA in 1971, scientists were able to develop useful and sensitive assays for reverse transcriptase of retroviruses by 1972.

The next major break came in 1976, when scientists discovered T-cell growth factor, or interleukin-2, which is necessary for long-term in vitro cultivation of human T cells. In 1979 scientists demonstrated for the first time that antibody
against alpha interferon slows significant increase in mouse retrovirus production by infected cells.

But in 1980 and 1981, these discoveries of the 1970's led to the first fundamental human analyses, including the isolation and characterization of the first human retrovirus, called human T-cell leukemia virus type I (HTLV-I).

While these discoveries were occurring in the laboratories, epidemiologists were in 1981 and 1982 documenting the outbreak of a fundamentally new disease in groups of young homosexual men. They called the disease "Acquired Immune Deficiency Syndrome" - AIDS as we know it today.

At a 1983 scientific conference in Cold Spring Harbor in New York, scientists for the first time linked a human retrovirus, tentatively identified as the HTLV-I or II variant, as the cause of AIDS. Further research reported in 1983 at the Pasteur Institute in France confirmed that a major protein associated with the HTLV virus caused immunoprecipitation of antibodies against this protein.

Finally, in 1984, Dr. Robert Gallo of the National Cancer Institute and Dr. Luc Montagnier of the Pasteur Institute in France announced their independent but interlocking discoveries of the HIV-1 virus.

With the introduction of the Western blot technique for clinical detection of these antibodies in May of 1984, confirmation of increasingly effective tests for these antibodies was reported throughout the remainder of 1984.
By the mid-1980's, then, the focus of scientific endeavor was rapidly moving from the identification and explication of the AIDS disease to the integration of these scientific breakthroughs into AIDS drug and vaccine development.

Section 4.4 - Statistics and Trends of AIDS As A Disease

International - According to the World Health Organization, by January of 1989 there were 377,000 reported cases of AIDS in 140 countries around the world. The United States of America leads other countries in both total cases reported, approximately 85,000, as well as in highest number of new cases reported. France is the second highest country reporting AIDS cases, followed by Uganda, Brazil, West Germany, Italy and Kenya.

In regional terms across the world, Africa leads in total AIDS cases reported with approximately 200,000, while North America reported about 110,000 cases. Perhaps as many as 40,000 cases have occurred in the Caribbean/Latin America region, while 25,000 cases have been reported in Europe and perhaps 1,500 in Australia, New Zealand and the Pacific islands. Curiously, only about 500 cases are reported in all of Asia.

However, the World Health Organization warns that the officially reported cases of AIDS represent probably fewer than half of the true number, for perhaps 5 to 10 million persons worldwide may already be infected with the HIV virus. Without new contrary evidence, most of these infected individuals are
likely to develop AIDS within ten years of initial HIV infection. Based on the guesstimate of 5 million cases of HIV infection worldwide, researchers at the World Health Organization estimate that perhaps ultimately 2.5 million of the AIDS cases will occur in Africa, 1.0 million in the United States. In addition, perhaps 750,000 cases will occur in Latin America, and 500,000 in Europe.

While internationally the HIV infection was initially concentrated among homosexual individuals, the spread of HIV in Africa appears to be primarily through heterosexual intercourse in urban areas. This development creates great fear in the Third World. Reports indicate that among sexually active Africans from the ages of 15 to 45 years of age, perhaps 5 to 10% of these persons in Kinshasa, the capital of Zaire, carry the HIV virus, and perhaps more than 20% are similarly infected in Kampala, capital of Uganda, with comparable numbers estimated for the Zambian capital of Lusaka and the Rwandan capital of Kigali. As a result, the incidence of HIV infection among newborns in Africa is also escalating.

For closer to home, the Federal Center for Disease Control (CDC) estimates that by the beginning of 1989, over half of the estimated 85,000 AIDS patients in America have died from the disease, including 80% of the patients diagnosed before 1985. According to a detailed study by the CDC in July of 1988, 63% of the victims of AIDS had been homosexual or bisexual men without any history of intravenous drug abuse, while 7% were
homosexual or bisexual men with a history of such intervenous drug abuse. Another 19% were heterosexual men and women who were also intervenous drug abusers. Almost 3% of the American AIDS cases resulted from transfusions of AIDS-contaminated blood or blood products, nearly all of which products had been received at their point of use prior to the advent of serological screening of blood donors was instituted in 1985.

According to the CDC's 1988 study, of the approximately 4% of American AIDS cases involving heterosexual transmission of AIDS, 62% of these persons had a history of sexual contact with a person documented as having been infected with HIV or with a person in another high risk category. Another 39% of these heterosexual cases involved AIDS cases among individuals born in African nations in which confounding factors, such as differences in the particular virus and in sexual practices, may exist. The primary mode of AIDS contraction is through heterosexual transmission. The ratio of men to women in the overall group of heterosexual AIDS cases are 3.5 women for every 1 man, a fact that the CDC attributes to the large pool of potential male AIDS-virus carriers in the United States, especially in the intravenous drug abuse and homosexual communities.

Yet clearly the fastest growing group of AIDS victims are children. In the July, 1988, report period, the CDC notes that cases of children with AIDS has increased 114%. Most of these cases are unfortunately linked to their parents' intravenous drug abuse, in that 78% of these children contracted
AIDS during the birthing period. Sadly, however, 19% of all children's cases of AIDS occurred as a result of blood transfusion or treatment for hemophilia.

In ethnic terms, the CDC reported in July of 1988 that whites made up 59% of adult and 23% of child cases of AIDS, while blacks represent 26% of adults and 53% of children with AIDS. Hispanics constitute 14% of adult cases and 23% of children with AIDS. Black and Hispanic rates of AIDS infection were disproportionately higher than their respective population shares (11.6% for Blacks and 6.5% for Hispanics). The CDC suggests that these trends reflect higher reported rates of AIDS in black and Hispanic intervenous drug abusers, their sex partners and their children. Similar disproportionate rates on an ethnic basis do not appear for adults in transfusion-associated cases, though the rate for black children is significantly higher, perhaps due to transfusions to manage low birth weight in black newborns.

By early in 1989, certain distinct changes were occurring in the epidemiology of AIDS. Fully 23% of all AIDS cases among adults and children are now linked to intravenous drug use, a significant increase from the estimated 18% in the 1982 when AIDS cases were first closely followed. Unfortunately, 4 out of every 5 AIDS cases linked to intravenous drug users sharing needles have apparently occurred among blacks and Hispanics. While more than 60% of all American AIDS cases to date involve gay men, analyses of data from 1968 through 1988 indicate that perhaps the gay male incidence rate for AIDS has
flattened out at a level of perhaps 7,000 new cases anticipated each year. But cases of AIDS among gay men are no longer clustered primarily in the early onset cities of New York, San Francisco and Los Angeles. Now perhaps two-thirds of new AIDS cases among gay men are reported outside these three cities.

The tremendous fears of contracting AIDS from casual encounters (i.e., kissing, accidental transmission of saliva, biting in children or using public toilets) have been completely discounted by experts. The CDC reports that in the study of more than 400 family members, with tens of thousands of daily household contact, not one person has contracted AIDS without having been sexual partners or been children born to an AIDS-infected mother.

The widely accepted best estimates for trends of AIDS infection in the United States of America suggest that the rate of infection with HIV virus is on the order of 1.5 million Americans, with perhaps 365,000 of these persons becoming AIDS victims by 1992, with perhaps 263,000 deaths occurring by that time. The impact of these estimates on private health care costs, including insurance claims and uninsured expenditures, as well as upon Federal and state health care budgets, may be the most dramatic public policy issue of the early 1990's.

A glimmer of hope emerged in late 1988 when The Los Angeles Times reported that its own analysis of AIDS trend data indicated that the growth of the AIDS epidemic appeared in 1987 to slow significantly in the Los Angeles County, San Francisco
and New York City areas, the American metropolitan areas struck earliest and hardest by AIDS. In particular, The Los Angeles Times suggested that its analysis indicated that these declines occurred primarily among gay white men, reflecting the probable impact of the community and government-sponsored educational programs aimed at promoting safer sexual practices.

We turn now to a discussion of research directions in the search for an AIDS cure.
CHAPTER 5

A SUMMARY OF CURRENT RESEARCH DIRECTIONS
FOR AIDS-RELATED DRUGS

[Because of the rapid developments in scientific research, this chapter provides only the framework and latest draft of the final "status" chapter which will be inserted into the text just before press time]

Section 5.1 Background on Federal Research Efforts

According to the 1988 report from Congress entitled "AIDS Drugs: Where Are They?", the major Federal AIDS drug testing program is conducted by the National Institute of Allergy and Infectious Diseases ("NIAID"), one of the National Institutes of Health. By the fall of 1985, two years after the discovery of the HIV virus as the infectious agent for the disease of AIDS, and four years after the first AIDS cases were reported, the NIAID issued the first request for proposals for extramural clinical research on AIDS-related drugs. The initial group of 14 contracts was awarded to principal investigators in June of 1986. These contracts went primarily to NIAID's AIDS Clinical Trials Units ("ACTUs"), which are located at academic and medical centers across the country. The ACTUs evaluate the safety and efficacy of antiviral and immune modulating substances and therapies for the treatment of the HIV infection, as well as specific therapies for the treatment of opportunistic infections (e.g., pneumocystis]
carinii pneumonia) and malignancies (e.g., Kaposi's Sarcoma) associated with the HIV infection.

In addition, the National Institutes of Health has established an AIDS Drug Discovery Program, where the National Cancer Institute has primary responsibility for preclinical drug discovery and development. NIAID has the subsequent responsibility to design clinical trials to test new AIDS drugs in patients. The National Cancer Institute's preclinical drug development program has the capacity to screen 24,000 compounds annually for antiviral activity. Drugs with demonstrated potential for AIDS-related therapeutic effects from animal studies are then referred by investigators (usually from within the Federal Government) to NIAID for review.

A dramatic example of this Federal approach was the identification in September, 1986, of AZT (now called zidovudine) as a potentially effective AIDS therapeutic agent. Subsequently approved less than one year later (March, 1987) by the FDA, AZT has demonstrated life-prolonging effects. While AZT was the first and to date only AIDS drug approved by the FDA (alpha interferon has recently been approved for the treatment of Kaposi's Sarcoma, a primary symptom and early opportunistic malignancy associated with AIDS), AZT can be highly toxic when taken over long periods of time, for it appears to seriously inhibit the production of red and white blood cells, requiring concomitant blood transfusions. Manufactured by the Burroughs Wellcome Company, AZT has also been
controversial for its extraordinary expense, which can cost thousands of dollars a month in treatment.

By the end of 1988, the FDA had granted treatment IND status to eight drugs, including the AIDS-treatment drugs trimetrexate and gancyclovir.

Section 5.2 Antiviral Drugs

Although hundreds of drugs have been developed to fight diseases caused by bacteria during the past fifty years, only a few effective agents for the treatment of viral infections have ever been developed. The primary reason for this disappointing record is scientific, not bureaucratic. Antibacterial drugs interfere with the biochemistry of bacteria alone and do not harm the human host cell or cell structure. Viruses in turn replicate within human cells. Because viruses use normal human cellular processes to reproduce, specifically inhibiting the replication of the virus without also destroying the human cells as well is quite difficult.

In addition, the HIV virus is a retrovirus, a class of pathogenic substances for which a therapy for their human impact has never been found. Since there is no current prospect for developing a drug that will eliminate just the infected cells, drug development is focusing on blockers of receptors and receptor-mediated infection, inhibitors of viral replication, immune system boosters, and therapies to treat opportunistic infections.

The antiviral drug category, which includes chemical and biological products intended to stop an existing infection from
progressing into a degenerative stage, has a variety of different search paths being explored by dozens of development firms and hundreds of noncommercial research institutions around the world. The screening of compounds for use in fighting viruses is particularly difficult in the case of biologically derived compounds, since both the starting material and the physiological and genetic makeup of the human recipient will vary. Purified, consistent starting materials for screening of potential drug therapy use can be achieved by biotechnology means, and AIDS research has benefited from genetics research skills developed on other drug projects in the past few years.

Prior to the appearance of AIDS, the field of cancer research had the most visible and active therapy priorities in medical research. AIDS has surpassed cancer in the urgency of financial commitments to new drug development, but the two fields are closely linked and each benefits from the other's research efforts. Studies of experimental cancer drugs which can inhibit the growth of the human but formerly rare type of cancer, Kaposi's Sarcoma (a primary symptom of active AIDS), and studies of AZT and alpha interferon have demonstrated that these drugs have potential anti-HIV effectiveness.
Section 5.3 Alpha Interferon and Kaposi's Sarcoma

The November 21, 1988, approval of alpha interferon for Kaposi's Sarcoma (named for the Hungarian dermatologist who described it in the 19th Century) indicated the degree to which cancer research on the category of interferons has benefited the AIDS patients. Primarily known as a non-fatal skin cancer that afflicted mainly elderly Jewish men of Eastern European ancestry, a more lethal form of Kaposi's Sarcoma has been endemic among young males in tropical Africa. Now, a yet more virulent version of Kaposi's sarcoma is the unfortunate hallmark of incipient or actual AIDS in many young male homosexuals.

Alpha interferon was demonstrated to be successful in clinical trials of carefully selected Kaposi's Sarcoma patients in their very early stages of AIDS, with no other opportunistic infections and still-functioning immune systems. In the key trial, some 45% of the 350 participants experienced tumor regression and prolonged survival. While solely for the treatment of Kaposi's Sarcoma, this clinical experience has encouraged researchers at the NIAID to explore alpha interferon's potential for use against the HIV virus itself.

Sporting different trademarked brands of alpha interferon, the Schering-Plough's Intron and Hoffman-La Roche's Roferon quickly entered the marketplace for treatment of Kaposi's Sarcoma in December of 1988. The Hoffman-La Roche product emerged from research done for that company by California-based Genentech, Inc., since 1978. Schering-Plough's version was cloned in 1980 by
Biogen NV in Zurich, Switzerland. Though versions of the same molecule, these two products differ by a single amino-acid. The Schering version of the molecule has an additional methionine moiety, for a total of 166 amino acids as against La Roche's 165. Both are purified by affinity chromatography, using monoclonal antibodies. Sensitive to the political controversy over the cost of AZT, both alpha interferon manufacturers announced $9,800 annual limits on the cost of their product's therapy. Available only by prescription, alpha interferon is nonetheless administered by disposable syringes for self-injection.

Section 5.4 Antiviral Drugs: The Promising Few

AZT is the only drug approved for the treatment of the AIDS disease. Alpha interferon as been demonstrated effective at present only for treatment of Kaposi's Sarcoma, while aerosol pentamidine has been approved for use under a treatment IND for pneumocystis carinii pneumonia. In addition, in early February of 1989 it appeared that the FDA might reverse its December, 1988, decision to preclude the marketing of gancyclovir, which is used to treat AIDS patients with cytomegalovirus, a pernicious viral infection that causes retina damage and ultimately blindness as well as debilitating intestinal inflammation. FDA previously allowed gancyclovir to be distributed by its manufacturer, Syntex Corporation, under a treatment IND. FDA may in the near future permit more widespread testing and use of a number of other drugs that show significant promise of success against AIDS, pursuant to
the investigations to be supervised by the new director of the National Cancer Institute, Dr. Samuel Broder.

**Dextran Sulfate** - Administered in the past as plasma expanders, anticoagulants and cholesterol-lowering drugs, dextran sulfates are large, sulfated, negatively charged molecules that have shown promise in inhibiting HIV replication, perhaps by inhibiting viral binding. Dextran sulfate works particularly well by inhibiting the formation of syncytia, which are giant, multinucleated structures that form when HIV-infected cells fuse with uninfected cells. An early AIDS clinician, Dr. Donald I. Abrams, is experimenting with dextran sulfate in Phase II trials at the San Francisco General Hospital.

**Soluble CD4 (rCD4)** - The human body has a class of white blood cells known as helper T cells, which are crucial regulators of the body's immune defense system. The HIV virus' envelope has a glycoprotein (e.g., gp120) that forms a powerful bond with another glycoprotein called CD4 (also known as T4), which is found widely on the surface of the helper T cells. These helper T cells with CD4 glycoproteins thus become a prime target of the HIV infection. When these helper T cells are sufficiently depleted or rendered dysfunctional, then the body is open to all types of opportunistic infections or malignancies which otherwise are regulated by the body's immune system. AIDS as a disease is then well underway.

As a result of this molecular biology of the HIV virus, one approach to fighting AIDS is to develop a free floating form.
of CD4 that can be available to the HIV for binding, thus monopolizing the available binding sites on the HIV virus and thereby keeping the HIV from binding to CD4 sites on healthy helper T cells. This complicated process may be best be understood by an analogy to locks and keys. IF CD4 is a lock, the experimenter may use the small peptides to flood the system with extra keys.

At least two different companies, Biogen NV and Genetech, as well as three research groups, including the Smith Kline & French Laboratories, the Dana Farber Cancer Institute, the Basel Institute for Immunology, and Columbia University have produced soluble CD4 through recombinant-DNA methodologies, demonstrating some promise currently in Phase I trials.

ddC, ddA, ddl - The drug AZT comes from a family of chemicals known as dideoxynucleosides, which also includes 2',3'-dideoxycytidine ("ddC"); 2'3'-dideoxyadenosine ("ddA"); and 2',3'-dideoxyinosine ("ddl"). These molecules are nucleoside analogues, in that they closely resemble the nucleotides that serve as the primary construction of DNA and RNA. Dideoxynucleosides are also reverse-transcriptase inhibitors, which is to say that they can inhibit the viral replication process of retroviruses.

The theory behind this action lies again in the molecular biology of the HIV virus, which first binds to a human cell and then fuses with that cell's membrane. After accomplishing this task, the HIV then injects its contents into the cell's cytoplasm. Once within, the inner protein coat of the HIV is partially withdrawn to expose the viral RNA of the HIV virus.
The basic thought behind a dideoxynucleoside's effectiveness is to act at this vital point to disrupt the subsequent viral replication or reproduction by blocking the action of the enzyme reverse transcriptase in the synthesis of the virus' DNA. Hence their designation as reverse transcriptase inhibitors.

ddA in its triphosphate form is a potent HIV inhibitor in animal tests, but in the human body ddA is often converted into ddl by the unfortunately seemingly every-present enzyme adenosine deaminase. ddl does not act strongly against HIV in the body, for in its phosphorylated form it appears only weakly active against HIV.

ddC, on the other hand, has been shown by researchers at the Stanford University School of Medicine to be quite effective in clinical trials with severely ill AIDS patients. These Stanford studies show that ddC can be effective by significantly reducing the amount of HIV reproduction through viral replication, with the added benefit of apparent improvements in the body's immune functions. However, ddC patients using the drug for more than eight to twelve weeks in continuously high doses developed peripheral neuropathy, primarily in the feet, affecting their peripheral sensory and motor nerves in that region of the body.

ddC is now in Phase II trials, both alone and in concert with AZT, in hopes of decreasing the peripheral neuropathy by alternating doses with AZT. ddA and ddl are both in Phase I trials.
Phosphorothioate Oligodeoxynucleotides - This class of chemicals are another example of possible reverse-transcriptase inhibitor. First suggested by Paul C. Zamecnik of the Worcester Foundation for Experimental Biology, this class of chemicals may disrupt the activation of the HIV cell by precluding its transcription and translation of viral DNA into viral proteins for viral replication. This chemical has shown some promise in Phase II trials, and is appears useful in treating cytomegalovirus, another opportunistic infection common among AIDS patients.

Gancyclovir - Cytomegalovirus is also being treated with another investigational new drug, Syntex Corporation's gancyclovir. Used extensively by AIDS clinicians for years under a "compassionate use" policy, gancyclovir has never been tested in a comprehensive clinical trial, though thousands of patients have received the drug. In December of 1988, the FDA refused a Syntex petition to market gancyclovir based on this extensive but anecdotal history of use, requiring instead that a comprehensive clinical trial be conducted. This study began in January of 1989, but by February massive pressure had developed for immediate widespread sales of gancyclovir in light of extensive reports of its effectiveness in stopping the spread of the cytomegalovirus across the eye and into the retina, which eventually results in complete blindness in the patient.

Gancyclovir is injected intravenously on a daily basis in order to suppress the cytomegalovirus. Unfortunately,
gancyclovir suppresses white blood cells, and many patients cannot use gancyclovir and AZT at the same time.  

**Castanospermine** - After HIV's viral proteins are produced, certain of these viral proteins in their final modification before emerging in a complete and functional HIV virus, add carbohydrates in a process called glycosylation. In this process enzymes add sugars to the protein and then some of the terminal sugar groups are trimmed from the protein by a group of enzymes called trimming glycosidases. By interfering with one of these trimming glycosidases, a plant alkaloid called castanospermine may impact on the HIV virus' ability to form syncytia or to infect cells. Castanospermine is now in tentative development and undergoing laboratory testing.  

**Interferon-Related Drugs** - A number of interferon-related drugs, including the alpha interferon that was discussed above as a treatment for the AIDS-symptom malignancy, Kaposi's Sarcoma, are also being explored for their AIDS-therapeutic effect. Ampligen, an interferon inducer, shows the greatest promise, with large-scale Phase II and Phase III trials now under way. In addition, a drug now used as an antiherpes agent, acyclovir, may also be useful in dealing with AIDS, particularly in concert with other AIDS drugs.  

**Other Drugs** - Phosphonoformate, Rifabutin and the long-tested Ribavirian are other drugs that are in one form of testing or another in the AIDS fight, either as possible reverse-transcriptase inhibitor (e.g., Phosphonoformate and Rifabutin), or acting in as yet unclear methods of partial anti-HIV impact (e.g.,
Ribavirin). Many other compounds and agents are being screened in laboratory-based testing to assess potential anti-HIV activity through a variety of scientific theories. Indeed, the emerging and perhaps greatest promise in the treatment of AIDS may lie in a combination of antiviral drugs, rather than the miracle "silver bullet" single remedy.

Section 5.5 Vaccines

Vaccines are among the greatest miracles of medicine. Diseases such as smallpox and polio were virtually wiped out over time by effective vaccination strategies, while yellow fever, measles, mumps and rubella are in dramatic decline due to the influence of vaccines against them. Perhaps one of the finest announcements in medicine is the announcement of a new vaccine.

Yet Surgeon General C. Everett Koop has warned the American people not to expect an vaccine against AIDS in this century. Perhaps the biggest obstacle to an effective AIDS vaccine is the absence of a good animal model. Such an animal model would provide a research environment in which to explore the insidious nature of the HIV virus, which hides in the human host cell or changes its protein coat with the goal of ultimately inserting its own genes into the genome of its human host cell. The animal model process carries with it the controversies over transgenic spread of diseases from animals to man; the ability to confine new infected animal species to a laboratory; and the issues of animal welfare concerns. It is possible that geneticists could impose the
human immune system into the "nude" mouse, a species with no thymus
gland and no hair, in future experimental breeding.

Without an effective animal model, the ethical dilemmas of testing vaccines in human clinical trials, with the guaranteed trial and error problems, deter most vaccine development efforts.

The objective of an AIDS vaccine will be to prevent the development of active HIV infection upon exposure of the vaccinated person to the bodily fluids of a person infected with HLV. When combined with disease-avoidance methods such as condom use and selectivity of sexual partners, the vaccine will help relieve the fear of disease among the widening range of persons who are at risk of transmission of the HIV infection.

Achieving that objective begins with recognizing the limitations of the vaccine. No vaccine is 100% successful in humans, and no vaccinated persons can assume that they need no longer apply preventive measures which may avoid the heightened risk of contracting the disease. If current medical literature on mucus membrane transmission of the HIV virus is correct, then the highest exposure circumstances occur with receptive anal intercourse without the use of a condom, and use of a hypodermic needle containing blood from a previous needle user (e.g., during intravenous drug use by several users of a common hypodermic needle). The limitation of a vaccine is that one who cares to avoid infection must combine vaccination with the avoidance of the highest risk sexual and injection patterns.
Human immunodeficiency virus (HIV) is the main focus of much of today's AIDS research. The ideal pharmaceutical "magic bullet" could be injected into the blood stream of the person who is already infected with human immunodeficiency virus, and would inactivate the HIV particles so that growth of the active virus and its subsequent side effects would be stopped.

The scientific search for an AIDS vaccine is extraordinarily complex. The briefest summary would state that the substitution of an inactive particle which resembles the virus, but does not do the damage which HIV can do, is the primary focus of current research. Smithkline Corp. began work on such a "Decoy" of the body's T4 cells in January 1989. The vaccine would be "tricking" the body's systems into accepting the less harmful particle so that, when and if the actual virus appears, the body would have been ready to respond and fight off the attack of the new and hostile particle. Advances in electron microscope research enable the virologists to study behavior of the components within the blood stream. This enables medical researchers to make more educated choices among the different kinds of biotechnologically derived particles which could, in many persons, generate the body's defensive immunities against the future appearance of the HIV virus.

Four basic types of vaccines are currently under study. The most famous approach, using killed whole viruses in a manner similar to that used against polio, is being studied by Dr. Jonas Salk under the California "fresh start" initiative discussed in
Chapter 2 of this book. Salk's method involves using killed whole or damaged yet theoretically inactivated HIV virus with its genetic material removed.

The second, perhaps most popular method, explores the use of a piece of the HIV virus, or a subunit as researchers call it, to create an antigen that would act to stimulate the body's immunological "memory" cells to attack the HIV virus upon presentation. The principal antigen being used is the HIV envelope protein or pieces of these proteins, with an adjuvant (e.g., a chemical that stimulates the development of the antibody). The first attempt of this approach was that of MicroGeneSys' subunit of gp160 that uses the chemical alum as an adjuvant. Indeed, the specific adjuvant utilized with the principal agent may prove to be the key element in a successful vaccine.

The third, and to date most successful, AIDS vaccine approach lies in the use of an HIV subunit in a virus vector, such as an attenuated cowpox virus. Many of the vaccine candidates using this approach use a subunit based on an internal component of the HIV virus rather than an envelope protein antigen.

Finally, certain researchers are exploring an anti-idiotype vaccine candidate strategy, wherein the goal is simply to develop an antibody to the CD4, the glycoprotein which is found widely on the surface of the helper T cells. These helper T cells with CD4 glycoproteins become a prime target of the HIV infection. The goal of this vaccination strategy would be to develop an antibody that would preempt all of these CD4 glycoprotein sites.
where the HIV virus attaches to the T helper cells, thereby precluding HIV fusion with the human cell, rendering the HIV virus unable to invade the human host cell for replication.

Some scientists are discouraged from the quest for an AIDS vaccine by the potential that the HIV antibody may be uptaken into macrophages, increasing these harmful macrophages because of the presence of the HIV antibody that had been delivered by the vaccine. Yet at least twenty different private companies, academic laboratories, and research institutes are involved in one of these types of AIDS vaccine development. While some of these efforts involved laboratory or limited trials, most of these approaches will encounter their most difficult moments as human trials begin.

The chapters of this book dealing with drug development and clinical testing provide more detailed explanations of the difficulty of making the right choices in an AIDS vaccine, particularly from the standpoint of the ethics of human trials.

However, while we discussed the limitations imposed on AIDS vaccine development due to the absence of an acceptable animal model, recent discoveries that the Macaque monkeys can become infected with HIV-2 offers hope that this species will be able to replicate the impact of the HIV virus in a manner that is transferable to humans.
Deaths in HIV-infected patients from opportunistic infections such as pneumonia are common, perhaps to be expected, if medical research does not develop the needed medications. The deaths are not from HIV infection itself, but from the weakened immune system's inability to deal with infection from viruses known as opportunistic infections. These invaders include fungi, bacteria and other viruses that take the "opportunity" presented by the loss of the body's T-4 defensive cells and expand into active infections.

The susceptibility of the body to these viral infections results from the body's "immunocompromised" condition, in which the T-4 cells of the immune defense system, normally responsible for stopping the infection by generating defensive or "immune" reaction particles, are depleted by the HIV attack. The fewer the T-cells, the more likely that there will be active diseases resulting from contact with the disease particles to which people are constantly exposed from other persons or casual contact during everyday life. So the medical research goal of eliminating the HIV infection's internal damage must be accompanied by study of how physicians can rapidly detect and treat viral infections which impact on the patient who lacks the natural body defenses.

Great success has now apparently been demonstrated in treating one of the worst opportunistic infections associated with AIDS, pneumocystis carinii pneumonia, which affects more than 60% of all AIDS patients. In its aerosol form, the drug pentamidine
appeared in preliminary data from clinical trials to decrease by about tenfold the incidence of recurrence of pneumocystis in patients who are administered the drug after they have recovered from one bout of the pneumonia. Yet in late 1988 researchers at Sloan-Kettering recommended that the aerosol pentamidine not even be tested as a therapy for active cases of this pneumonia. Their primary concern stemmed from a British study of thirteen patients where the failure rate in the use of aerosol pentamidine was 75%.

Notwithstanding this British data, the FDA announced on January 31, 1989, that aerosol pentamidine would be made widely available, perhaps to between 50,000 to 100,000 individuals with AIDS or pre-AIDS immune system abnormalities, through the treatment IND process. The FDA's decision was based on a study (unannounced at the time of the FDA's decision) conducted by Dr. A. Bruce Montgomery, Dr. Gifford S. Leoung, in concert with other San Francisco General Hospital physicians working with a group of community physicians in San Francisco with substantial AIDS patient caseloads.

This San Francisco study, whose preliminary results were reported at an AIDS conference in Stockholm in June, 1988, showed that a monthly 300-milligram pentamidine treatment (administered as an aerosol) was highly effective both in preventing initial cases and even recurrences of pneumocystis carinii pneumonia, perhaps the most feared complication of AIDS. The study had tested three different dosage levels of aerosol pentamidine over an 18-month period. The 300-milligram treatment on a monthly basis
achieved the highest level of impact, which was reduced incidences
of relapse of pneumocystis carinii pneumonia, as compared with
doses of 150 milligrams or 30 milligrams every two weeks. Indeed,
the predicted rate of relapse was 60%, but the overall relapse rate
following administration of aerosol pentamidine at the three dosage
levels was found to be only 10% The relapse rate for the least
effective dosage level appeared to cut the relapse rate in half,
or down to only 30% from the predicted 60%. Mortality rates during
the San Francisco study were only about 4% for all patients,
including all three dosage levels.

The pentamidine was prepared for administration by
dissolving pentamidine powder in sterile water, and then the
patient inhales the resulting mixture through a inhalation device
such as the Respigard II nebulizer that disperses the pentamidine
as a fine mist.

LyphoMed Inc., located in Rosemont, Illinois, was granted
the treatment IND by FDA primarily to allow the company to recover
their research and development costs by charging patients, which
was not permitted during the clinical trial. However, LyphoMed may
not promote or advertise the drug prior to FDA's granting a new
drug application for aerosol pentamidine.

Nonetheless, under the treatment IND, LyphoMed may not make
available aerosol pentamidine to two basic groups of patients:
those with AIDS who have already had pneumocystis carinii
pneumonia, and pre-AIDS patients who have never had this
opportunistic infection but who have tested HIV-positive and whose
T-4 helper cell count is below 200 or below. LyphoMed has since October, 1984, been permitted to market an intravenous dosage form of aerosol pentamidine for the treatment of pneumocystis carinii pneumonia. The pricing for aerosol pentamidine is not yet set, though the charge to pharmacies for the intravenous dose was about $100 per vial, indicating a higher charge to patients.

Section 5.7 Drugs For Cancer Symptoms

The drugs being developed for the cancer symptoms of patients with human immunodeficiency virus will pay dividends for all cancer patients. The infectious nature of viruses which may cause certain cancers, the delayed onset of cellular growth of the hostile virus in both AIDS and certain cancers, and the prospect of interrupting patterns of the "out of control" cell growth are all common elements of both cancer and AIDS.

As noted earlier in this chapter, the anti-cancer drug alpha-interferon was on November 21, 1988, approved for Kaposi's Sarcoma, a serious cancer which was formerly rare in the United States but which has been associated with many active AIDS cases. The interferons, a class of drugs with activity in the cell and sub-cellular level of the blood and tissue, offer great promise for cancer remedies. Alpha-interferon approval received a high priority from the FDA and was a "fast track" drug product as it went through the approval process.
More rapid, more certain and less expensive test kits for the detection of human immunodeficiency virus are being developed in laboratories around the world. The urgency for protection of the supply of human blood led to research results in this aspect of AIDS research, and the need for detection capability on short notice and at lower costs has spurred a continuation of active research.

Cambridge Bioscience Corporation received approval in late 1988 to begin sale of its 5 minute Recombigen HIV-1 LA (AIDS) test in the United States, following more than 7,000 clinical uses during tests performed in nine locations throughout the country since February 1988. This test kit is based on a recombinant protein, CBre3, that is a fusion of the most reactive or "immunogenic" regions on the outer coating of the HIV virus. The test is known as the latex agglutination test kit, in that it utilizes microscopic latex beads coated with the genetically engineered CBre3 protein. This testing approach may eliminate the more risky process that rely on use of live AIDS viruses grown in a cell culture. While not well adapted for mass screenings, this test may prove most useful in the Third World medical settings that often lack well-equipped medical facilities.

In a separate but potentially related action, the FDA approved in late 1988 three separate tests for the detection of antibodies in blood to the HLTV-1 virus, the precursor retrovirus discovered by Dr. Robert Gallo of the National Cancer Institute and
initially believed to be related to the HIV virus, in that it has been linked to adult T-cell lymphoma cancers.

African nations in particular need the less expensive detection methods which require less technological sophistication in the detection laboratory. Their epidemic of AIDS among heterosexual persons has exceeded the limited capacity of the medical care system. Integrity of the blood system for transfusion is especially difficult. The current U.S. evolution of more precise initial tests for HIV infection will benefit the African and Third World countries whose prospects for AIDS preventive measures will be greatly enhanced by improvements in the available detection methods. With a worldwide AIDS screening market estimated at $100 to $150 million annually currently, and likely to double in the next five years, the competition to provide these HIV-detection methods will be keen.

Section 5.9 Nutrition and Maintenance

No reputable AIDS researcher believes that food alone will "cure" AIDS. But the maintenance of the dietary strengths of HIV-infected persons may be a factor in prolonging life, and perhaps may postpone the activation of the HIV particles which often lie dormant for years. Herbs such as shiitake mushrooms and garlic have been studied; positive nutrition therapies may be needed as the person loses appetite and becomes weaker as a result of the disease process (or, in some cases, as a result of the medications used to fight the infection).
Further studies of the combinations of vitamins, herbs and other nutrition products are currently underway and are expected to show some potential benefit in future research.

Section 5.10 Problems of Research

The problems of AIDS research run the gamut from a lack of resources to frighteningly simple disasters to legal uncertainty. Fiscal Year 1989 funding for NIAID drug discovery research totaled $22.4 million, in support of 28 separate groups. President Ronald Reagan's final budget proposal suggested a 30% across the board increase in AIDS research and education efforts.

On December 8, 1988, the simple act of turning off the power at a National Institute of Health laboratory for maintenance work resulted in the death of the only colony of mice genetically altered to carry genes of the AIDS virus in every cell.

Uncertainties over the legal liabilities for the occasion when a health person contracts AIDS from the use of a licensed AIDS vaccine has led some companies to insist that the Federal Government should assume all liability for AIDS vaccines, as it did in 1976 with the vaccine for swine flu. These proponents suggest that the 4,000 lawsuits and over $100 million paid out in swine flu damages is a graphic illustration of the problems companies developing AIDS vaccines will face. Such legal consequences may they argue, preclude companies from taking the risk of bringing promising research to market.
Critics of this view argue that the marketplace for AIDS-related vaccines would be so large as to provide sufficient cash flow to finance insurance coverage, even self-insurance approaches. Congressman Henry A. Waxman, chair of the House Subcommittee on Health and the Environment, argues that

The payoff is so great for a company that can develop a vaccine that the incentive to go forward with research is overwhelming. Removing the liability would only increase what is already an enormous profit potential.

CONCLUSION

The search for a cure to AIDS through AIDS-related drugs will go forward, notwithstanding the early defeats and problems that plagued the effort.

The adoption on October 21, 1988, of a new FDA rule permitting significant acceptance of risk by the patient and the attending physician in the study of new investigational drugs (see Chapter 13) argues strongly that AIDS has fundamentally altered the regulatory theory of life-threatening drug research and development.

Whether in response to the mere advent of the disease we call AIDS, or to the reaction in the form of a rising critique of government that crested in the form of California's "fresh start" initiative, or merely as the predictable shift in paradigm that must occur for scientific change, the response has indeed changed the drug development regulatory world as we know it. We turn now
in the second half of this book to explore the how and what of this change.
CHAPTER 6
How Government Regulates Health Products

Section 6.1 Principles of Categorization: When is a Product a Drug?

Beauty is said to be in the eye of the beholder; "drug" legal status is in the mouth of the manufacturer. The words the maker uses for a description of its product in oral sales presentations, written brochures, product claims accompanying the product and in the label make the product a "drug". The label is not the lone messenger. The product can be classified by FDA as a drug because of the claims made in many different ways over and above what the label has said. Unless the manufacturer concedes that the product is a drug (which occurs in the great majority of cases), the FDA will resolve uncertainties by collecting the labels, the brochures, tapes of public lectures and other evidence about the claims made before it reaches an official finding that the product is a "drug".

For example, a product which is routinely used for specialized animal care in pet stores might be labeled for that use only. A person or company which believes that this material may also have benefits for one of the symptoms associated with HIV may circulate a flyer recommending that persons with that condition try
it. The FDA could treat the animal care product as a human drug because claims made for the product show an intent that people use it for a drug benefit. The FDA could enforce the new drug application requirements of the law against vendors of the product who made such claims. If the person making the statement had absolutely no connection to the sale of the product but was merely expressing an opinion, and if the sellers of the product did not make use of that opinion to expand their sales, then the courts might decline FDA's invitation to treat the product as a drug. The more controversial areas, such as HIV issues, draw considerable FDA attention.

Section 6.2 "Drugs" and "New Drugs" Defined

The Food Drug & Cosmetic Act allows FDA to regulate as a human drug product, any item to which any one of three requirements applies:

(1) a claim of benefit for disease therapy, cure, prevention, diagnosis or mitigation is made;

(2) the product is intended to "affect the structure or any function of the body of man"; or

(3) the product is officially recognized as a drug in the three major pharmaceutical reference works which provide drug information to prescribers and pharmacists.

In the case of a product directed to the AIDS illness, there are few products in category (2) and perhaps none in category (3). Most of the FDA coverage (and most of the disagreements) will
come in category (1) above. A label of a bottle of mixture XYZ will say, "helps prevent the spread of the AIDS virus", or a lotion will be labeled, "use this before contact with a person who carries the AIDS virus." These claims bring the product within the "drug" definition even if the products are of no drug value at all.

Historically, when disputes over drug status have gone to court, FDA has been given broad authority to regulate such products if the court believes that the consumer will expect the product (based on claims made about it) to prevent a disease, diagnose the presence of the disease, cure or lessen its effects, or treat its symptoms.

Not all drugs are "new drugs". A more complex formula applies to deciding which existing drug products require specific FDA approval of their effectiveness and safety, as "new drugs". History and opinion are the two standards.

Historical pedigree of a very old drug such as Listerine removes it from the prior approval requirements which apply to "new drugs". Once a product is legally a drug, e.g. because the chemical's owner claims that it lessens the symptoms of pneumonia, it may be a "new drug" if it lacks a history of prior use or if it is not yet "generally recognized" as being safe and effective ("GRASE").

The historical standard for avoidance of "new drug" regulatory clearance was only a political compromise. The 1938 Act and the 1962 amendments allowed then-existing products to be excused from proving their safety and their effectiveness. In the
HIV drug situation, no products prior to 1962 had labeled their ability to affect the as yet unknown HIV illness. So there are no historically old drugs which are legally able to make HIV treatment claims.

The second category, "general recognition", requires that a drug become known to the community of experts in a field such as immunology. As a result of these experts' knowledge and experience with the drug, the drug may be classified as "generally recognized as safe and effective" and it is thereby exempted from the lengthy proof of effectiveness and safety which other drugs must establish.

If the drug product for HIV is neither historically exempt nor recognized by experts as GRASE, then "new drug" status applies. It is unlikely that any drug which the sponsor labels for HIV treatment will escape the "new drug" category.

Section 6.3 "Medical Devices" Defined

The medical device category can best be seen as the "other side" of the drug definition. A medical device has the characteristics of a drug, with each of subcategories (1), (2) or (3) in the preceding section, but it does not operate by being metabolized, so it does not deliver a chemical effect in the body or on the skin.

The medical device may be inert, mechanical or electrical in nature, or it may have some chemical action "in vitro", outside the body. But it does not break down and deliver a chemical to the body. For HIV products, the well known ELISA antibody detection
kit is a medical device because its chemical diagnostic function occurs outside of the body, in the laboratory. The catheters used to provide nutrients to an ailing patient or the equipment used to conduct neurological screening do not have any chemical effect, but they are intended to be used to mitigate and diagnose illnesses. So they are regulated as "medical devices" by the FDA's preclearance and classification schemes.

In a very few cases, medical device and drug status may be confused. FDA is gradually clarifying the distinctions. In some cases, the claims made for a generally available consumer product link that product to an HIV prevention role. For example, facial tissues are consumer products. If the tissue were sold with a leaflet which promises that its user will prevent any AIDS infection by use after sexual contact exposure with an HIV-infected person, the tissue would be a medical device because its intended use of disease prevention is a medical device claim.

Section 6.4 Vaccines and Biologics Defined

The federal laws which regulate disease prevention vaccines have been in force since 1902, when they passed Congress during the era of yellow fever and smallpox. Vaccine product regulation is extremely specific, tightly controlled and research-oriented, to a greater extent than drug regulation. It is managed by the Center for Biologics Evaluation and Research of the Food and Drug Administration.
A vaccine is a product derived from living organisms, such as human serum or blood products, with properties intended to immunize a recipient from the infection or condition. In the context of HIV, a vaccine could enter the blood stream and could generate antibodies against the later appearance of the HIV virus. Antibodies are the natural defensive mechanism of the blood, and the vaccine stimulates their growth.

When the research and production difficulties are overcome in the future, an HIV vaccine will be licensed by the FDA after assessment of laboratory experiments, field trials in healthy patient volunteers, and specific factory and vaccine licensing by the FDA. Biotechnology is likely to be used to develop a safe vaccine product, such as a vaccine derived from hybridoma. In the case of polio and swine flu, some vaccines were made from "killed" viruses in which an inactivated strain of virus is produced in a form which promotes growth of antibodies without causing the appearance of the live virus. Chapter 14 discusses this at greater length.

The FDA also regulates other "biologics", products which are derived from blood products and which are used by humans. For example, blood and plasma sold by a blood bank are regulated as biologic materials. FDA creates standards for the collection of blood, for storage of blood products and for creation of blood-derived serums. Blood testing safety standards for HIV detection are stringent and becoming more so as new tests are developed. Blood transfusions, antibody fractions and materials
used for allergy treatment are among the biological products which the FDA licenses.

Section 6.5 Detection Assays and Diagnostics

FDA regulates chemical and biological detection media and kits as diagnostic products. These products are medical devices. Their effect occurs outside of the body; they are labeled for diagnosis of diseases; and their manufacturers intend that they will have value to the physician in the interpretation of a disease condition.

FDA's review of these products comes under the medical device approval authority of the Center for Devices and Radiological Health. This is addressed in Chapter 15.

Section 6.6 Medical Foods

Eating a normal diet will provide normal nutrition for the uninfected person, but HIV-infected persons may have special maintenance and strength promotion product needs. For some patients, a special dietary need exists for supplementation of the diet or special means are needed for delivery of the nutritive foods. An enhanced level of carbohydrates in a special mixture for a patient who is losing weight, for example, may be directed by a physician. These specially-formulated products are medical foods. Other hospitalized persons may need enteric nutrition delivered by tubes, where the swallowing and digestive functions are not operating properly. These are also "medical foods".
FDA's control of medical foods is in a state of flux. The "pure" vitamins are exempted from much regulatory control because of 1976 legislative amendments. The normal food products have the ability to make health claims on labeling, subject to some controversial regulations which became operational in 1988. And Congress has not given FDA any clear message about how it should regulate nutritional products apart from those which are clearly "drugs".

Because the regulatory situation is not well settled, a nutritional product which claims to provide the "AIDS prevention diet" or a special combination of vitamins which reduce the risk of developing HIV symptoms will fall into the FDA-regulated drug category by virtue of their claims.

Section 6.7 Orphan Drugs

A special class of "new drugs" are given special consideration by FDA because of their risky economic position. The Orphan Drug Act of 1982 addresses an unusual problem in drug product development. The potential exists that some new drugs which have medical benefits will not come to market because their development would not pay back the large investment needed to proceed through testing and New Drug Application approval. These drugs, for relatively rare disease conditions, would become "orphans" in the marketplace.

Orphan status means that the drug gains government financial incentives. The individual physician or organization
developing a drug could apply for money grants from the FDA. The larger drug firms have special tax credits awarded on certifications by the FDA, reimbursing them with tax credits for the development cost of the drug for a rare condition. And the orphan products maker wins exclusivity for its products for a period of time after product approval.

In the HIV situation, some of the symptomatic conditions associated with Stage IV symptoms (under current medical definitions of HIV consequences) are of relatively infrequent appearance. AIDS has many manifestations which are "out of the mainstream," so there is a basis for awarding to developers of drugs for these conditions special rewards. These rewards, allowed by the Orphan Drug Act, include both preferential financial treatment and the encouragement of exclusive approval status. These products' status is no different because of orphan designation, since the product remains a "new drug" and it must still demonstrate its effectiveness and safety by means of clinical studies.
CHAPTER 7

THE APPROVAL PROCESS FOR DRUGS - OVERVIEW

Section 7.1 - FDA's Operation of the New Drug Application

Requirements

Most drugs which are effective for AIDS-related conditions are "new drugs" in FDA parlance. A "new drug" (as defined for FDA purposes in the preceding chapter) requires a "New Drug Application" ("NDA"), a multi-volume submission of documents, research data, study results, manufacturing processes and other technical information. Unlike some governmental forms which can be completed in a few minutes on one page, the assembly and delivery to FDA of a completed new drug application may require dozens of managers and scientists working over several months to compile reports. The end result is a small truckload of papers which cumulatively fill a large storage room.

FDA's decision process on new drugs is oriented to maximum data collection. Recently, FDA has modified its new drug application rules to reduce the volume of papers actually delivered, and FDA experiments are underway for delivery of NDA submissions through electronic access to a computer data base. In response to the trend for greater statistical analysis of patient care results associated with new drug effectiveness studies,
computerization of the testing files is a definite advantage to FDA and the drug sponsor.

The complexity of the law's operation has principally been affected by the requirement for "adequate and well-controlled studies" (plural) of product effectiveness. One is not enough, except in rare cases. The drug product approval process requires that the studies in human subjects follow after initial studies in animals; that both sets of effectiveness research be conducted under scientific controls to verify the accuracy of the results; and that possible conflicting factors which might affect the study outcome, e.g. more female subjects on the drug than on the "control" standard product, be anticipated and avoided through careful drafting of the study protocol.

Congress delegated to FDA the power to designate which studies are "adequate" and which are "well controlled", and FDA uses this power in different ways depending on the drug, the risks, the size of the studies, and the attitudes and practices of the individual FDA medical reviewers. These two aspects of study operation involve professional judgment and discretion. FDA judgments are virtually never overturned on the rare occasions when drug makers seek review of FDA's disapproval decisions in the courts.

The stages of new drug approval are described in detail in the subsequent chapters. In general, FDA uses the law's broad delegation of powers to examine the drug's safety and effectiveness. But FDA also focuses attention on the quality of
manufacture, the chemical formulation and analysis to be undertaken for the new drug, and other elements which are important to showing that the sponsor can be expected to make the drug correctly for a prolonged period of time. When these stages are completed, FDA also checks the label claims and the initial advertising (in the case of a prescription drug) to become aware of how the drug's marketing may affect the patients and prescribers.

A new drug applicant cannot afford to forget that Congress gave FDA power over more than just the human study phase of drug approval. Before, during and after human research steps, FDA has a continuing oversight of the research. Ignoring the FDA's expectations and guidelines, at any of the phases of approval, risks a rejection of the application. The HIV drug products developed by smaller companies with less FDA experience are particularly susceptible to such problems.

Section 7.2 Legal Requirements for New Drug Application Approval

Federal Food, Drug & Cosmetic Act authority for the use of the New Drug Application (NDA) process affords the FDA a great deal of flexibility. The application documents must be submitted to FDA prior to the commercial distribution of the new drug into the marketplace. FDA's approval letter declares the NDA "effective" as of a certain date. This letter is a legal prerequisite to commercial sale, and monthly lists of approvals are made public by FDA. Each approval letter is specific to one
product, made by one manufacturer, with one or more product claims or disease "indications" listed on the approved labeling.

The law requires the applicant to bear the burden of demonstrating that the product is "safe for use" and "effective in use". This proof must survive critical scrutiny by the FDA. Courts tend to uphold FDA when the agency decides that the applicant has proven safety or efficacy.

Among the law's requirements, later fleshed out in great detail in guidelines and regulations, are submissions of animal and human test results; chemistry data on active and inactive ingredients; manufacturing details; and samples of the drug. The law requires FDA to review this information and make a decision within 180 days after NDA submission. In practice, few are determined within that time limit. Most are found "incomplete", withdrawn, resubmitted, and recycled around the 180-day clock again until approved or finally withdrawn or rejected.

Procedurally, the new drug application sponsor has the burden of proof. The law sets out reasons why FDA may deny the application. Then the sponsor is entitled to an opportunity for a hearing. After winning disputes over the interpretation of this language in several court cases, FDA has taken the legal position that an applicant must be able to show, before the hearing, that it has enough new evidence which would win the legal approval if the hearing were to be held. This means that FDA controls which drug products are given hearings, so FDA can refuse to hold a hearing if the NDA sponsor's supporting documents (which FDA
requires to be filed with the request for hearing) do not contain sufficient support for approval of the product. This procedure sounds like prejudging the outcome of the hearing before it is held. Courts allow FDA to do summary denials of hearings as a way to speed the agency's product approval process.

Section 7.3 What is "Safe"?

FDA's definition of "safe" for a drug means a low incidence of adverse reactions or significant adverse effects under use conditions which follow the product label's adequate directions for use and warnings. The drug's absence of harmful consequences in human clinical trials will form the basis of this safety conclusion.

The decision that any drug is safe requires consideration of the risk-benefit ratio which is acceptable in light of the product's label warnings. FDA has been delegated the authority to decide this risk-benefit ratio. No drug is presumed fully safe regardless of its age or experience, but many products are known by experience to be safe when used under proper directions, with adequate warnings or in limited settings.

Since any drug is potentially harmful at some large dose, it is very important that safety be related to product dosing. Dosages of the product which are not adequately "safe" are usually calculated during animal studies and Phase I and II clinical studies. A drug which could be injurious by overdosing is approved
as "safe" when adequate label directions limit the likelihood of such an abuse.

In the case of a product intended to treat HIV-infected individuals, "safe" means that the drug does not have an unreasonably high level of adverse effects upon patients treated with the drug during the clinical trials. A product could be unsafe, at least in theory, if it were ineffective for its therapeutic purposes and also posed some small risk -- for then the risk-benefit equation would not support its acceptance for human use. In most cases, denial of approval on the basis of safety will come when the HIV-related drug produces an undesired side effect which is out of proportion (in prevalence or severity) to its expected benefit for the general population of HIV-infected persons.

Section 7.4 What is "Effective"?

The law limits FDA's flexibility to consider a product "effective", even when prestigious physicians have used a particular drug on their patients with consistently favorable recoveries or mitigations of disease. The law requires the proof of adequate and well-controlled human clinical studies which establish a statistical conclusion that the products are effective against the disease, when compared to the "control" group of similar patients who received either another drug ("active control") or an inactive version ("placebo control").
Effectiveness decisions require statistical data, and the courts have upheld the refusal of the FDA to accept anecdotal experience as a substitute for scientifically verifiable data. The data almost always comes from two or more human clinical studies conducted at different sites within the United States, although in rare cases (such as a large Norwegian study of the heart drug propranolol), one well prepared foreign clinical study might be accepted. The effects of the drug are considered according to the claims made on the labeling. A product which claims a 20% reduction in the lesions associated with HIV-infected patients' skin infection must be able to show that amount or more to convince FDA that the tests adequately establish 20% reductions will occur in use. A product which could be shown to be effective for two related drug indications, but for which only one indication is claimed, is officially found to be effective for only one indication, but the sponsoring company could use its research to later qualify the second indication through a supplemental new drug application.

In the case of a product intended for the treatment of HIV-infected individuals, "effective" will probably mean a level of reduction of either the symptoms (e.g. PCP pneumonia) or the activity of the virus within the body of the infected person. This effectiveness will be statistically established in two clinical trials of several hundred patients, at doses which are expected to be effective. Because of the great public attention to these trials, FDA will probably insist that a comprehensive set of
accuracy safeguards be built in to the proof of effectiveness in
the design and conduct of the trials.

Section 7.5 Comparative or Subjective Claims

Drugs may be approved by FDA as safe when they are shown
to be safe on their own merits, regardless of what other new or old
drugs may do. Their approval may be hastened by FDA's recognition
that the particular drug is also comparatively safer than the
alternative, existing drug product. Comparative studies with the
two drugs may be part of the later phases of clinical studies.
Designing an appropriately scientific and "fair" comparative trial
can be quite difficult.

Even if clinical data is developed, FDA usually does not
allow drug sponsors to make comparative claims for the
newly-approved drug's safety compared to other drugs. In some
cases, a very relevant factor such as comparative safety of
infrequent side effects which exist with the drug will be permitted
to be included. But claims of safety, and to a lesser extent claims
of relative superiority of an approved new drug compared to another
drug, are generally not permitted by FDA in drug labeling.

The average user does not realize that such a general
prohibition on drug product comparative claims exists, since
over-the-counter aspirin comparisons have been televised for years.
The advertising of such "old drugs" sold without a prescription is
regulated only by the Federal Trade Commission. As far as FDA is
concerned, a "new drug" sold only on prescription should not be
advertising its comparative safety except with the concurrence of FDA's drug advertising office, whose disdain for comparative advertising (other than of price) is legendary.

Subjective data about experience with an experimental drug can be developed during "treatment IND", "compassionate IND" or foreign marketed use of the drug product. When a drug product is already approved for sale in the U.S. and a prescribing physician decides to use it for an HIV-infected person, anecdotal experience about the drug gained in this way could be interesting but would not be allowed as a basis for NDA approval. The point of the 1962 legislative amendments was to exclude anecdotal experience and instead to force the decisional process into channels which would generate scientifically reproducible results. This legislative decision may appear to frustrate HIV infected persons who learn of the benefits of a new treatment, but would be required to await its scientific proof.

Section 7.6 Chronology of an Approved Drug

It may be useful to understand the typical timing of the drug approval process through the use of a hypothetical HIV-related drug product. Private sector research, whether commercially initiated or (less frequently) supported by National Institutes of Allergy and Infective Disease (NIAID) grants, begins the process. FDA does not perform the testing of the drug; it receives and reviews data which private developers have generated with the help of private or university testing facilities.
This chronology will use a hypothetical drug, ABC, which is intended for HIV-infected patients who could develop cryptococcal meningitis (CCM), a potentially fatal fungal infection which may be associated with HIV infected persons. The chronology will roughly estimate the process of drug approval. Because criticism of the drug review process has focused on FDA review times, when in fact the delays outside FDA for HIV drugs are considerable, it is important to begin the focus at the private sector's first decision point for compound ABC. Only much later will FDA approval become even possible for this drug.

On day 1 of year 1, ABC, the compound intended for use against the disease CCM is first selected as a candidate for animal screening. Scientists working on a CCM project found it among a group of 100 other compounds of possible value. Using computer analysis of potential chemical compounds, looking for candidate compounds which might have effects, the pharmacologists and chemists of the sponsoring company decided to develop ABC among a group of 20 chemicals. Along with compound selection, synthesis of the chemical may be quite difficult, because the sponsor's laboratory group must prepare a sufficient quantity of the "pure" chemical in order to be able to open the testing process.

In year 1, day 120, maximum tolerated dose (MTD) screening with ABC is done first in a small number of rodents. That lethal dose figure sets the upper limit for future administration of ABC, and for the safety factors which will be used for human ingestions. Human doses will be kept well above the
"safety factor", a multiple of the number which is the human body equivalent of that dose which killed the lab animals. An animal study protocol is prepared and a test request is prepared. Animal testing laboratories discuss the proposed testing, agree on the project and protocol, and receive the test compound in year 1, day 210. A protocol, like a road map, guides the test lab's selection of animals, doses, and other details of testing.

A short-term toxicity study is completed and reports received on day 1 of year 2. Because ABC has a structural similarity to a chemical believed to cause cancer at certain doses, a two-year animal feeding study of the compound's safety is undertaken as a precaution by the sponsor. This is completed and a report is received on day 120 of year 4. The full Investigational New Drug Application is ready to be submitted because preliminary results from the 2-year animal testing had shown no sign of cancer related to the dose of ABC. (A well-known existing product for which no cancer potential exists might skip over this stage of testing.)

The sponsor is ready and eager for human studies to begin, and the phase I human study site has been selected with a willing investigator in place and ready to go. The IND is filed on day 180 of year 4. (By law the sponsor proposes the test and then waits 30 days before beginning the study.) FDA calls with additional questions on day 205 and places the IND on "clinical hold". After a further submission, the FDA allows the IND to go forward on day 250 of year 4.
Healthy human volunteers in the Phase I testing group serve as a test of the basic safety of ABC and as the source of blood chemistry indicating how ABC will dissolve in the body and how it will find its way to the areas of the brain in which neurologists believe the CCM disease flourishes. The desire is to have the person who is in good health act as a model to show the physiological absorption of the chemical within the body. This is often done with low-dose radioactive tracing versions of the product. Sophisticated monitoring equipment can be used.

Phase I healthy volunteers then receive the drug ABC. It shows no major side effects. At some time during year 5, the IND is updated to show the results of Phase I and the commercial decision is made by the sponsor to proceed with the drug's further development. Phase II studies begin, after a short clinical hold which might have been avoided by better presentation of the data.

These Phase II studies are the first time that an HIV-infected person will receive the new ABC compound. It is likely that meetings with FDA will be necessary to resolve the questions raised by the reviewing Medical Officer about the protocol design. Informed consent is particularly tricky for the HIV related drug products, as discussed in Chapter 7.

At day 120 of year 6, FDA meets with the firm to discuss the statistical findings and the medical assessment of patient condition noted in Phase II work. Several months are spent planning Phase III clinicals and setting up the investigators who will run these large scale human studies in their university
clinics. The IND amendment for Phase III permission is again held up until questions are resolved. Both large scale studies begin in year 6. (Chapter 9 details the FDA's 1988 "short-cut" regulatory procedure for the highest priority AIDS drugs in order to move them more efficiently through the process.)

At the end of year 7, FDA and the firm meet and the FDA is given a preliminary view of the results. This was a successful Phase III larger scale testing of hospital patients suffering from the CCM condition associated with HIV infection. The firm is ready to submit the New Drug Application; FDA suggests some additional data compilation among the thousands of data points produced. Three months later, the NDA is filed. It is declared "incomplete" five months later. Then the firm must rewrite the manufacturing controls section of the NDA, prepare a different statistical assessment of one of the reactions noted subtly in the clinical studies, respond to deficiencies found after a week-long FDA inspection of the manufacturing plant, and modify the labeled indication (disease condition, here CCM) to more precisely characterize the use of the drug in situations of suspected CCM.

The NDA is officially resubmitted as amended at the end of year 8. FDA's special review priority, the "1-AA" classification (because ABC is intended for a symptom of AIDS, the indication of CCM) speeds the review process from the reviewing Medical Officer through five higher levels of approval: division director, office director, center director, and for the most visible HIV related products, Commissioner and Secretary of Health
& Human Services. The latter two, when and if involved, may have no specific technical input but will merely translate the decision to approve the drug into terms useful in news media publicity and Congressional explanations.

In mid-year 9, the final FDA questions about the substance of the New Drug Application are resolved and paper labels are ordered. The sponsor receives an "approvable" letter for ABC which orders changes in ABC's printed labels. The advertising drafts submitted to the Prescription Drug Advertising branch are rejected and negotiated, and a much milder set of advertising claims is allowed. At day 270 of year 9, final agreement is reached at a meeting and the labeling is accepted. A joint press conference by FDA and the maker of ABC is held on day 320 of year 9, which announces the approval of the drug and that it will be shipped immediately. Cumulatively, decisions to short-circuit the process could have reduced this normal clearance time by about four years.

The FDA portion of the pre-approval process is completed at this point but post-approval reporting to FDA of adverse reactions (including failures of efficacy greater than the norm anticipated) is also expected. The chronology is not complete. The firm must get a Drug Enforcement Act "controlled substance scheduling" if there is a danger that ABC may be habit-forming. And the firm must obtain the concurrence of Medicare officials and state formulary officials, who determine which drugs are reimbursable for patients receiving public assistance. Because CCM
is a serious and perhaps fatal condition, its cost of hospital care and pharmaceuticals is likely to be borne by public assistance for many of the persons infected with HIV.

Finally, the firm will ask the Patent Office to extend the 17-year term of the ABC patent (which in this hypothetical case had issued in year 3) so that an FDA-acknowledged period of drug product regulatory review can be financially "recouped" through Patent Term Restoration Act procedures. Where the drug is for a rapidly evolving medical condition, the pursuit of exclusive rights to sell ABC by extending patent terms some 15 years into the future may be a legal right, but it probably will not be a real financial benefit, since HIV-related products will likely have a short "life cycle" before their replacement with superior technologically altered products.

ABC has endured to approval, but along the way, 100 other compounds which also began the process during year 1 month 1 have been dropped, have failed to win FDA approval, or have been withdrawn because of safety problems or absence of proof of effectiveness. The chronology of the steps gives the reader an understanding of how difficult it would be to bring an HIV-related compound to the market, even without the 1-AA "fast track" which FDA permits for products related to the AIDS illnesses.
Section 7.7 Principle Suggestions for Change

The community of HIV-infected persons and their advocates have criticized the delays in the drug approval process. The Presidential Commission on the HIV Epidemic, in the Chairman's Draft Recommendations of June 1988, and a variety of other reports, have expressed the frustrations of infected persons with the drug review process.

The time delays inherent in the process of FDA drug review also have been vigorously criticized by advocates for cancer patients in the lengthy litigation of "laetrile" and other cancer cures, cases in which the courts tried to resolve conflicts between a conservative statutory scheme for approval and the reality of desperate patients. But AIDS-related conditions, and especially HIV-infection, pose an urgent situation even more dramatic than the cancer cases. In the case of unapproved lung cancer cure claims, some remissions have occurred and the disease patterns appear to have been understood more readily than the newly-recognized problem of HIV infection. The AIDS problem is quantitatively more devastating to younger persons and qualitatively more puzzling than some kinds of cancers.

Suggested changes to allow the faster operation of the drug process include more conditional approvals with active monitoring of the adverse reactions in the marketed drug population; broader based clinical trials among thousands of patients with fewer controls or patient qualification criteria for
test subjects; and approvals of a safe drug for an AIDS indication with less stringent demonstration of product effectiveness.

Conscious political and legislative tradeoffs must be made if these suggestions are to be considered further. Development stages of IND Phases I, II and III lengthen the total time before a drug is made available for the HIV-infected persons at large. But the extra time of effectiveness testing adds to the assurance that the product will work for those who receive it, and the recipients are more likely to benefit as a result of the marketed products. The Presidential Commission on the HIV Epidemic's recommendations did not advocate changing the law. But it would be necessary to make statutory changes for alteration of the product effectiveness criteria for drug approvals. FDA chose, instead, to work without changes to its basic law when it developed its 1988 "fast track" procedures.
CHAPTER 8

Stages of the Approval Process

Section 8.1 - Origins in the Bench Research.

This chapter gives an overview of the approval phases which are explained in detail in the later, more specific chapters. The reader may find this synopsis a useful roadmap to the later discussions.

The search for a cure or prevention of the HIV infection found in AIDS cases begins with chemistry. The design of the right chemical molecule which is expected to provide the therapeutic or preventive benefit is a matter of both inspiration and perspiration. Chemicals are often found by searching among related, known compounds, for those compounds which have been considered but not adopted for particular purposes. The chemist searches the known literature and the known collection of existing chemicals, in search of a potentially promising linkage between a particular type of chemical activity and the therapeutic direction in the body for which the drug is being selected.

The design phase of drug research is extremely important to making future decisions about the drug molecule or compound. A very large investment may be made in animal research, with a conclusion that the drug is ineffective, when in fact a very small modification of the compound could have made the difference in a
much more effective product. It is important that the chemical designer be sensitive to the need of that particular chemical to deliver that particular physiological activity in the particular body organ. For example, the HIV virus causes certain neurological damage to the brain. By studying the chemistry of fluids around the base of the brain, the pharmaceutical chemist can determine whether a particular type of compound is likely to increase the resistance of the brain fluid to the detrimental effects of the HIV virus. Therefore, in creating the appropriate chemical to be tested in animals and later in humans, the chemist attempts to determine which items will be both compatible with the existing body defenses and likely to promote a very positive contribution of the body's defenses against biochemical attach by the virus.

The design of a molecule or compound for use against AIDs is easier today than it was decades ago. Although scientists still try one at a time, there is increasing use of computers to perform structural design and structure-activity comparisons among alternative structures of chemical compounds. If a known therapeutic chemical works in a particular way in the blood stream, and has some effectiveness against diseases other than HIV virus, than a study of the effects of the HIV virus in the blood stream may suggest ways in which the existing well-known chemical can be adapted to meet the particular needs of the AIDS patient.

The great complexity of the AIDS virus and its slow development from virus into active clinical disease poses special design problems for the bench chemist. Drugs which have been well
established as effective against other viral conditions may not be effective against the most complex HIV modes of infection. These complex viral problems likely to be encountered with AIDS make it important that the design/selection process be closely aligned with the qualities desired at the end of the process. That is, the body must operate compatibly with the pharmaceutical chemical. The incremental benefit of the chemical may be to hasten the body's natural defenses to the appearance of the HIV virus. Or in some cases, neurotransmitters within the body can be studied, and the chemical needed to lessen HIV infections's neurological symptoms may be identified in a way which facilitates the protection of the patient's nervous system from the damage which can be caused by active clinical AIDS.

One of the additional complex factors involved in bench research is the microbiological request for a vaccine product. The bench research for a vaccine is different than that for a synthetic chemical since the vaccine products are made from living organisms such as microbes or microtechnology materials, and these properties determined in the living organisms are of a different caliber than the computer-projectable chemical structures. That is because the living organisms from which vaccines are taken are (like all living organisms) not as predictable as inert chemical substances.

The legal complexity of bench research involves the patent status of the chemical under discovery. The chemical may already be known, and be patented, so that a license fee would need to be negotiated with the owner of the drug patent. If the patent
holder is also engaged in AIDS research, the fact that a competing firm is willing to pay for the privilege of using that compound may be an undesired disclosure of one's research directions. Research into a patented drug occurs quite frequently, especially towards the end of the patent's life when generic drug companies are preparing their equivalent copies which might come onto the market after the patent expiration date. In the 1984 amendments to the Food, Drug, and Cosmetic Act, Congress permitted the generic drug companies to begin research and small-scale research-based production of a drug, all steps necessary to obtain FDA approval, without being considered in breach of the pioneer drug patent. This area of competitive use of the patented drug is a highly complex one, beyond the scope of this text.

Section 8.2 - The Animal Study Phases

An essential element of animal studies for the AIDS drug must be an understanding of the physiology of the disease in humans. From that assessment of the disease, scientists next tried to determine which model of animal would be appropriate. Different animals have different systems, especially the distribution of blood within the body and the creation of conditions which may be hospitable to the growth of the HIV virus. It is probable that no animals develop AIDS in the same way that humans do; it is essential that the physiology of AIDS be understood before an appropriate animal model for AIDS treatment can be designed.
Because human systems such as blood, liver, and kidney function differ from the corresponding systems within many animals, it may be inappropriate to take certain animal species as the appropriate models for future human use of the AIDS product. Selection of the study animal can determine the appropriate FDA response of the offer of animal studies in support of a company's proposal to investigate a new human drug. The FDA might reject the studies, ascertain that the animal study chosen was not representative of the potential effect in humans. FDA could assert that negative findings (no adverse reactions) in animals would be of value as a finding only if the animal model were in some way appropriate to demonstrate the propensity of the body to develop the virus, process the pharmaceutical drug, or otherwise show benefits as a result of the drug or vaccine product. The selection of the animal to be tested can be determined by examining what aspects of the body are to be affected in man if the drug is to be successful. Then, an animal model best representing that type of body system may be selected.

When considering which animal model to use, scientific literature about studies on this type of viral illness may be indicative. Summary documentation of the Food and Drug Administration approval of new drug applications for drugs in this category will show the types of studies which the sponsor had performed with this kind of chemical in the past, to the satisfaction of the FDA. Or the sponsor may disclose this information in the course of its discussion of how the AIDS drug
came to market. By whatever means, the discovery of the type of animal used assists the researcher not only in accessing what kind of animal model to use, but also what kind of animal model would be unacceptable to the Food and Drug Administration.

It is especially important that the correct animal type be used in rodents, since some breeds of laboratory rats have a genetic deficiency and spontaneously develop certain tumors or have certain congenital problems which pass along from generation to generation. It will be a complicating, difficult matter if the species of animal were to produce a spontaneous tumor or show birth defects results which would be attributable to the new drug product or vaccine itself. Such an incorrect assumption could be avoided if the proper animal type or breed were selected for the research, with understanding of the problems inherent in using any particular type of breed of rodents.

The animal study model is then tested with a maximum tolerated dose of chemical to determine the level of chemical or vaccine ingestion at which a certain number of the animals in the exploratory study will die.

This overdosing of the animals allows the responsible pre-clinical laboratory study to proceed by scaling back from that fatal dose to a more reasonable, less toxic dose. Because toxicity is a measurement of responses to certain doses, it is extremely important that the animal study be done with very high quality analytical results and with very good attention to the pathological examination of tissues from the deceased animals after the end of
the animal research. In the AIDS cases, it is especially important that the animal studies be done properly because the "fast-track" human study phase will be built upon accurate and fair preclinical evidence. Bad animal studies jeopardize the whole human drug program, for which they are the essential foundation.

Section 8.3 - Phase I Human Studies

The Phase I human clinical study is the most important safety measure within the drug approval process. A population of several dozen or 100 paid healthy volunteers participates in a clinical examination of the human body's toleration of the particular drug. These healthy volunteers are given the drug to determine whether they are likely to develop adverse reactions. They are also providing the measurement points for a human bloodstream dissolution of the chemical. Typically, the drug will be administered with a radio-active tracer element and the body of the human subject will be examined to determine how the chemical has progressed through the system. Also, blood examinations will be taken at periodical intervals during the day to determine how rapidly the chemical is breaking down within the bloodstream and is being absorbed by the body or excreted through the excretory system of the body.

It is important to emphasize that at the first stage of human research, the Food and Drug Administration insists that patient rights and informed consent be fastidiously maintained. FDA will examine the safety of the drug by reviewing the first
investigational new drug (IND) application submitted for that drug product. If the FDA is not satisfied with the adequacy of the animal studies, the adequacy of the human test protocol, or has other problems with the research, than the administration of the drug to humans will not be permitted. FDA will put a "clinical hold" on the IND. The sponsor of the drug experiment will need to go back and revise the test protocol or get other information in order to produce a human experiment which is satisfactory to the Food and Drug Administration.

In the case of AIDS, a very special problem arises. Healthy volunteers who are not currently testing positive for the presence of the antibodies related to HIV vaccine may be exposed to those antibodies in the course of HIV-related medical research. The safety information about the drug or vaccine is very important to society, but for the individual test subject who was healthy and who had no antibodies prior to the test, participation will render that person "positive" in future antibody testing. Therefore, the person should be given some form of permanent identification so that in future screening of persons for possible HIV infection the former research test subject is able to differentiate his or her antibodies status from that of persons actually infected with the AIDS disease. Indeed, in the event that a virus being tested in the form of a vaccine might cause an actual illness to the person, informed consent should be provided. (Chapter 14 discusses this issue in detail.) It is therefore likely that human volunteers will be more difficult to recruit for AIDS studies, because they
face both potential discrimination and potential infection with a catastrophic disease. This level of informed consent and counseling prior to undertaking tests might serve as a severe deterrent to willing participation of healthy volunteers in the study.

The best result of the human first stage study is that the drug does no significant damage to the organs or blood stream of the persons who participated in the tests, but the blood stream does indicate a beneficial, therapeutic or preventive level or the active ingredient from the drug. This blood stream effect is measured over time, to determine whether the drug product is likely to have its intended effect for the benefit of human patients. Without this initial human exploratory testing, research would not be able to demonstrate any appropriate dose of the drug product which will be safe for human use. If, on the other hand, the drug actually injures persons at a high enough rate, than the manufacturer probably will not proceed beyond these first-phase human clinical studies. It would not be fruitful for a manufacturer who found significant adverse effects in Phase I Human Clinical Studies to go on to Phase II, unless the need for the drug was very acute and the FDA were satisfied that the benefits of the drug clearly outweigh its risks for the particular patient population.

Because Phase I checks the safety parameters, and translates into human terms the levels of risk which were experienced in animals, this state of clinical testing is essential
for the future success of the drug product. Phase I tests of an
AIDS drug must be done right, and must be done promptly, in order
to meet the goals and desires of the large population who await an
effective AIDS drug product.

The FDA is generally cautious in approving human
experimentation, even at Phase I, with the most potentially serious
chemicals or vaccines. In the event that the Phase I study was
done overseas, the FDA may require repetition of that study among
human patients in the United States. Because the FDA is looking
to blood levels, details of adverse effects, and the like, the test
population should be one which is healthy and which is
representative of the types of persons in the United States who
will be in contact with this particular illness. However, patient
selection need not be as detailed at it will be for the Phase II
and Phase III studies.

In determining that a Phase I study was properly done,
the FDA is essentially agreeing with the manufacturer that the
appropriate level of blood stream effects of the drug have been
determined, that the adverse reactions are not severe enough to
cancel further human exploration, and that the drug basically
behaved the way it was expected to behave as the result of the
animal studies. If any of these three characteristics are not
found, than the consequences of Phase I might be to hold up the
drug product even further. It is not clear whether the FDA will
challenge a particular drug product until after the Phase I studies
are examined, statistics are derived, and plans for future studies

124
have been laid out. Protocols for patient selection, examination, and further study may come from a meeting with the FDA at the end of the Phase I. If the results are good, and the quality of the study is good, the drug will go on to the next Phase II.

Section 8.4 - Phase II: Safety Testing Among HIV-Infected Persons

When the Food and Drug Administration medical officer involved in the review of an IND for a drug examines the Phase II testing protocol, he or she is looking for adequate safety protection for the test subjects, and for reproducible, scientifically valid results indicating that the drug or vaccine will have the safety that it is intended to have. This second stage of experimentation will undoubtedly show some adverse side effects from administration of the drug or the vaccine. An abnormally high occurrence of serious adverse effects, or unexpected fatal effects, would be cause to abandon most pharmaceutical products. During the course of the Phase II study, reports are being made very frequently to the FDA reviewers concerning the appearance of unexpected adverse effects. The sponsor, when drafting the protocol, identifies as broadly as possible the "expected" adverse results which may be seen in patients. This reduces the number of reports that need to be made to the FDA during the course of the investigations of that drug.

The objective of the FDA reviewing medical officer during the course of meetings which precede the Phase II safety studies is to make sure that the data generated will be adequate. The data
must be scientifically valid, as well as fully documented, for the necessary conclusions to be drawn from the set of patients who are studied. Because this may be a relatively small body of patients (several hundred), it is critical that the clinical investigator must document those patients' experiences while on the experimental drug or vaccine. The experience, weighted to emphasize adverse experiences, must be adequately captured by the study records.

This safety phase of drug development is generally considered a major challenge to the scientific capabilities of the drug sponsoring company. Humans are inherently difficult to "control" during research. Phase II clinical safety studies are quite complicated, and require a great deal of attention to detail. It is very important that the sponsor of the drug study be able to demonstrate close adherence to the product testing protocol. FDA will be scrupulous in examining both the documentation and the conclusions. At the end of Phase II, the FDA will know whether the drug is safe in animals and humans, what doses seem to be more likely to cause adverse effects, and what the adverse effects are likely to be. This safety information is crucial as a precondition to moving the product forward into human effectiveness studies.

For the AIDS products, some Phase II safety studies will also involve effectiveness of the "fast track" drug. It is essential that the AIDS drug be tested among persons who actually have the HIV infection. The selection of volunteer patients for Phase II studies is crucial, since the FDA wants a reproducible and
valid finding. The pool of patients is impacted by large demand for trial participation, and the problem of confounding therapies.

Advocates for the community of HIV-infected potential test participants want the maximum number of eligible persons to participate as subjects of the research, but limited selection has benefits to the drug's sponsor. Selection of eligible Phase II patients is crucial for the economic success of the product, for its approval by the FDA would become doubtful if too many patients were brought into the clinical study at a stage of progression of the disease which made it likely that they would coincidentally die during the study. Each death during the study, while merely coincidental with the administration of the drug, would make it less and less likely that the product would win easy FDA approval. Therefore, a manufacturer or sponsor has an incentive to get the least infected cases, the most "healthy" set of infected persons, to participate in the Phase II study.

Safety testing of any drug among persons who already have the illness has inherent risks of making their illness worse. AIDS patients are often willing to accept those risks. From the point of view from the drug sponsor, it should be understood by the FDA that those persons already ill with the catastrophic disease may die with greater frequency than those persons given a drug for some more mild, longer-termed illness.

FDA's 1988 initiative to meld Phase II and Phase III studies into a "fast track" review process is a special case, developed for AIDS, which may succeed in breaking down the key
points of delay. More interaction and more pre-Phase II consultation by FDA will improve the work to done on all drugs.

Critics of the clinical study process have questioned the rationale for exclusion of women and children from AIDS clinical studies. In an October 5, 1988, press statement, the FDA explained that the serious toxic side effects of the chemicals which were being developed for AIDS kept most pregnant women and children out of trials, but women of childbearing age "who are not pregnant and practice a reliable method of birth control" are eligible. Trials are beginning in children, but the complexity of selecting test subjects is much greater with children, in that the sizes and health conditions of children vary so widely that a uniform dose of the experimental drug might be too strong for some.

Section 8.5 - Phase III Effectiveness Studies

This is the stage at which a drug must prove that it "works." The drug wins or loses approval because of the presence or absence of scientific clinical evidence demonstrating effectiveness. A product is not effective if it cannot show statistically sufficient improvement, compared to an alternate therapy or no therapy at all. The law, as amended in 1962, requires that the FDA determine the effectiveness of the drug through review of the sponsor's "adequate and well controlled studies." The purpose of these studies in Phase III is to demonstrate the product will be effective for the condition for which it is labeled or indicated.
FDA's 1988 initiative brought part of this effectiveness work back into Phase II's safety-oriented clinicals. Testing drug effectiveness through joint safety-efficacy analysis of larger populations of infected persons may prove to be the future strength of FDA's AIDS-related work.

Phase III begins with a conference between the sponsor and the FDA medical officer and reviewer. The FDA team has the data before it from both the animal and human studies, and has questions about whether the product should be tested in certain dosages or in certain sets of patients. The conference will produce questions and suggestions from the FDA. It is the responsibility of the sponsor to anticipate that FDA will want the studies to be done in a certain way, and to meet those suggestions either prior to, during or after the meeting. It would probably be futile for a sponsor of a drug to ignore the FDA's suggestions and recommendations for examination of a drug's efficacy. This is because the same reviewers will be in the same seats after the efficacy studies are completed, and the approval of the new drug application is an extremely discretionary (and scientifically complex) judgment call. Therefore, understanding what the FDA reviewers expect, and meeting that expectation, is the only appropriate way to satisfy these future hurdles to NDA approval. Drug sponsors try to get FDA's written concurrence about what tests or methods will be considered "enough" for approval.

The FDA drug reviewers will be interested in the controls which are built into the study. It is essential that the control
group which does not receive the proposed drug or vaccine receive some appropriate "blinded" alternative. "Blinding" means withholding the identity of the alternative so the patient does not know if he or she is getting active drugs or not. In the typical pharmaceutical test, a placebo control is appropriate, in which the test subject receives a tablet or pill made with sugars, colorants and fragrances similar to the prescription pharmaceutical in the "active" group. In the AIDS situation, however, because the persons in whom efficacy is being tested already have a catastrophic disease, it is more ethically desirable that an approved HIV-related drug such as AZT (zidovudine) be administered as the control product.

An effectiveness study would be fatally jeopardized if it were not able to show actual "blinding" of the results. The FDA guidelines consider a test "blind" if there is no way in which the patient can determine which of the two drugs the patient is receiving. To do otherwise would signal whether patients should expect results, and would thereby distort the outcome of the study. It is possible, for example, that the psychological benefit of knowing that you are receiving the "active" experimental drug may in some cases promote a psychological benefit which produces an observable medical improvement in the patient.

During the Phase III clinical, which may take one to four years, there may be several thousand test subjects who are receiving different doses of the drug at two to twelve clinical testing sites. Because the law requires FDA to make a finding of
effectiveness after examining the "adequate and well controlled studies," FDA typically requires two Phase III clinical studies. There have been situations in which this third stage has been accepted as one large study; typically, however, the FDA will require two adequate and well controlled studies of product effectiveness.

The FDA typically does not permit the sale of the drug to the investigational subjects, but in the later stages of clinical efficacy trials the FDA permits a sponsor to seek FDA approval for charging patients for the drug. In these cases, the FDA determines that the product probably will be approved, that the cost of producing the drug is very large, and that the test results will not be affected by charging the patients. Payment for the drug is to be an exception to the normal free distribution of the investigational drug.

Apart from free therapeutic drugs, the benefit for human drug patients from participation in the study is that the products that are made available to that HIV-infected person may be therapeutically "breakthrough" products which might produce a significant benefit for that person. Even if they are not, the seriousness of the AIDS infection is so great that participation is seen as a public service to the larger community of persons infected.

The great bulk of documentation of the overall drug study process is generated in these Phase III clinicals. The Phase III clinicals produce documentation in many volumes of patient case...
It is probable that a human clinical study for product efficacy in one clinical center may produce ten volumes of data on several hundred patient participants.

Section 8.6 - Approval and After

The product approval process does not end with the end of the Phase III clinical effectiveness studies. Rather, these effectiveness studies are added to manufacturing data, analytical data, labeling claims, the Phase I and Phase II safety studies, the other animal and human experience information, and compiled into a "new drug application" ("NDA"). The NDA is then submitted to the FDA.

FDA reviews the NDA data with great care, and conducts field inspections of the adequacy of the information. The FDA field inspections are usually quite exhaustive, verifying that the data was actually produced and that the record keeping was done appropriately. The process of NDA review depends to a great extent upon the priority that is accorded to the drug. Products are graded from one through five and with letters AA to E, depending upon their relative importance to medical science, and to the extent to which the product is considered "truly new" or "breakthrough". For AIDS related drugs, FDA assigns the approval priority 1-AA. This is the highest level of "fast-track" approval that the FDA can grant.
During the time needed for approval, the FDA is still updating the adverse reaction reports, examining any additional ongoing clinical studies and gathering further information from foreign governments, if any have approved the drug, or from clinical investigators who are interviewed by FDA field investigators during "good clinical practice" audits.

A drug which wins rapid review because of its higher priority status as an AIDS curative agent is likely to receive greater FDA attention to the post-approval process. The law does not give FDA authority to require post-approval studies. Most sponsors willingly agree to some post-approval reports, in order to expedite NDA approval. In the post-approval process, the FDA looks for unexpected frequency of adverse reactions, or unexpected adverse reactions which did not show up or which were not anticipated during the approval process. The FDA post-approval scrutiny is intense for AIDS drugs. These products require very cautious attention to insure that they are performing their vital role of addressing a catastrophic illness. Withdrawal is possible if the approved drug shows unanticipated problems in its early public dissemination.

Also subsequent to an FDA approval, a drug product may need the blessing of several other government agencies. The Drug Enforcement Administration may need to review the product, if it is deemed to be a "controlled substance" because it could be habit-forming. The Health Care Financing Administration ("HCFA") which is responsible for Medicare and Medicaid funding may be skeptical
about the use of this drug as an appropriate therapy. Because HCFA pays many of the bills for government-assisted patients, it is necessary to have HCFA approval of the product in the therapeutic context, in order to qualify that drug as an appropriate Medicare/Medicaid-covered therapy in the "Diagnosis Related Group" for handling these kinds of illnesses.
CHAPTER 9

The Animal Study Requirements for a New Drug

Section 9.1 - Selecting the Right Animal Study Model

The research to be done on an AIDS drug probably will pose an extremely complex challenge for the developer of animal research studies. The HIV virus from which the disease has been isolated manifests itself in a variety of symptoms. AIDS as a disease condition has several unanswered one viral questions and many manifestations in opportunistic infections. The right animal model for studying AIDS requires awareness of the differences in physiology between the humans who have been treated for AIDS and the animals which would be the subject of the studies. In order to know that the anti-viral compound (e.g., the material chosen to deal with skin disease symptoms) was appropriately tested in a certain animal species, scientists must study the species' blood circulation, history of use of virus materials, and biological characteristics of the species. The purpose of the evaluation is to determine whether this animal breed can be expected to develop symptoms of the HIV infection in a manner that is similar to patterns of disease seen in humans. It is important to preclude false reports or assumptions from the animal studies. The occurrence of the virus in a particular species of animal may be difficult to detect. But this phase of the investigation is
extremely important to having valid scientific evidence of the appropriate preventive or therapeutic entities which could be used.

Chimpanzees are, at the moment, the most promising animal model for AIDS research. HIV infection in the chimpanzee does not show the same progress, however, so this animal model is not perfect for AIDS research. No perfect non-human animal model has been found.

Complicating the search for the right model is the problem that not all species of animals are accessible even if they did appear "right" for HIV infection studies. Some species of animals are not available, because their species is endangered. In the situation of an endangered species, scientists would not have a sufficient pool of animals (e.g., a certain type of chimpanzee with a lung comparable to humans, for pneumonia tests). Too few would be available for experimentation with a new vaccine or pharmaceutical drug. The Federal endangered species legislation and its implementation by the licensing of breeders are a constraint on the selection of the appropriate animal model. If primate animals such as gorillas are necessary to testing a viral product, the National Institutes of Health or Centers for Disease Control would be an appropriate resource for help to get the viral research program going. Any animal use for vaccine or drug testing must, of course, be conducted with adequate professional and scientific care, minimizing pain to the test animals.

An important limitation on the use of small animals, such as rodents, is the appearance in some species of laboratory rodents
of spontaneous tumors at rates considered unusual. The chronicling of the generation-to-generation occurrence of tumors in these rodents suggests that for some types within the species, certain rodent breeds would show spontaneous tumors, and therefore may not be the appropriate animal model to be used. If the inappropriate animal is used, and cancer is detected in these animals at a larger than expected amount, the drug may be suspected of causing cancer, when in fact it is the animal rather than the drug which is the source of the tumors.

Section 9.2 Study Design and Protocols

A protocol is the road map of an animal research study. The nature of the test drug molecule is understood as a matter of chemistry, but the effects of the drug in animals are not well understood (except through analogy to other compounds of known history and known testing results). To design a drug study satisfactory to the FDA requires that the research design be prepared by an experienced, competent investigator. The findings of the study can be questioned if the investigator did not prepare an adequate protocol, or because of bad design or supervision the investigator did not follow the required protocols. It is essential that the experimentation proceed on a scientifically valid course, making use of the minimum number of animals necessary to be sacrificed for this scientific finding. Unnecessary or inappropriate use of animals, even when consumed for so large a human problem as AIDS drug development, is not ethical. Therefore,
the study design should use no more than the minimum number of test animals for the type of findings which are being investigated.

The format of a protocol depends upon the type of study being conducted. FDA's past acceptance, its guidelines, consultant advice, and published norms of protocol design, illuminate the choice of formats to be selected. The protocol is a very important road map and any deviation from that road map should be carefully documented to make sure that the subsequent audit of that animal study by the FDA will find that the execution of the intended study design stayed within its original protocol, or that change was properly documented for amendments.

Section 9.3 The Importance of Documentation

The AIDS drug developing company will have spent several hundred thousand dollars by the time the animal studies are completed. If the results was open to question, doubt and challenge, the money will have been wasted. If the FDA then refused to permit human studies of the drug, because the animal studies were not competently done or were poorly documented, then additional animal studies (with attendant delays) will be necessary, before the product can even reach its first human investigatory volunteers. For these economic and practical reasons, documentation of the animal studies is important to the final success of an NDA drug.

Standing alone, however, no animal study will actually support the final approved NDA drug. Animal studies are an
important foundation or building block for human studies. But they are not the end of the process -- merely the beginning. Few animal studies actually would be pivotal to the breakthrough drug product.

Most animal studies conducted will later be shelved, because the human clinical effectiveness or safety of the drug was not established and thus the test drug is abandoned. FDA insists that animal studies performed over three, six, twelve, or 24 months will be carefully documented so that the research will be demonstrably valid, whether or not it forms the basis for a breakthrough drug.

In the development of new drugs, problems encountered in the clinical phases may have been avoidable. For example, the non-clinical test evidence must be accurately recorded and accurately retained for future audits. FDA field investigations of laboratory studies look at both the records of the study and the physical evidence retained. Typically, slides of the tissues removed from the animal organ after its death are retained and evaluated by veterinary pathologists. These scientists examine whether or not the animal organs have developed lesions suggesting potential cancer associated with the dosing of that particular drug. Human cancers take so much longer time to develop that it is important to a cancer-related finding that the appropriate veterinary scientists examine the physical evidence of animal organ tissue, to determine the presence of tumors that would mean that the drug
may pose a potential cancer problem, unless an alternative cause exists.

For AIDS drugs, the documentation problem is especially acute. These high priority drug products may have had their non-clinical test evidence done more rapidly than such evidence might be done on another long-term project. After the animal study is done, the FDA will expedite the human research work and approval to be done on the AIDS drugs. Therefore, the "fast-track" approach to the AIDS drugs makes it very important that the quality of documentation for the non-clinical (animal) studies must be done appropriately. It would be tragic if the human studies were underway and showing promise when a field investigator found that the principal animal safety studies done on the drug could not be reconstructed because of significant failures by the testing laboratory. Any auditor's retrospective finding that the animal studies were not adequately documented could pose a threat to the entire research program on this particular chemical for use in the AIDS drug therapy program.

Therefore, documentation of the animal studies is essential. Cutting corners in order to get the drug into human trials more rapidly is counter-productive, jeopardizes the future NDA filing and exposes the testing laboratory to regulatory action up to and including prosecution for knowingly inadequate or falsely-prepared data.
The rationale for doing animal studies for a test drug is to determine whether humans can safely be given this drug at certain doses in human studies. Cancer is a special concern. The human system will develop cancer long after the rodent system develops tumors in the much smaller organs and blood stream of the animal. Therefore, dosing in animals will typically include an examination of the potential cancer effects of the drug. The animals are sacrificed (killed) at the end of the laboratory feeding period, or at the end of the animal's expected life, as defined in the protocol, to determine whether these internal organs and tissue have been adversely affected by the injection or feeding of the drug. The dosage that is used is carefully evaluated during the initial pilot phase of the study to find out whether there is a maximum tolerated dose above which the animals would die from an overdose of the drug product. This maximum tolerance or dose becomes the high point of dosing, and different levels of dosing below that point are then calculated. It is important to evaluate the safety of the product in relationship to the dose administered; even such common products as water or salt can themselves become killers when ingested in too great a quantity.

The scientific evaluators who examine the animal tissue after the end of the animal phase of research are looking specifically for indications that bodily organs were damaged by the presence of the chemical in the bloodstream. Viral infections such as HIV may be very difficult to assess in animal studies.
Side effects of the drug which shows promise as an anti-viral product, may be so severe as to end the appeal of that drug for a particular use. Toxicity of AZT, the first HIV-related drug, can be very serious to the patient's blood system. However, the study of the side effects of the drug may be useful by suggesting other uses of that product.

One ancillary benefit of the great investment in searching for an AIDS drug is that scientists may find that some of the "failed" candidate drugs will be effective for cancer, chronic illness or other diseases. For example, the AZT product was first tested as an anti-cancer agent and abandoned. Evaluation of safety of such a drug should take into account its side effects, balancing possible risks against these potential benefits.

The best result for an anti-AIDS drug is a conclusion by the veterinary pathologists, who have studied slices of tissue from the internal organs of the animal, that there is not evidence of cancer or pre-cancerous effects of ingestion. The evaluators should ideally find no injury to the systems of the animal at all. The animal studies should indicate that the product does not cause harm to the animals, or that if it does cause harm, it is only at such large doses that it overcomes normal defenses of the body system.
Section 9.5 Audits of the Animal Data

The animal study requirements for a new drug include the power of the Food and Drug Administration to audit the testing laboratory's compliance with the "good laboratory practice" ("GLP") regulations. The GLP structure is the framework within which all U.S. laboratories should produce scientifically valid, FDA-acceptable studies of the effects of a drug. It is expected that if the same set of animals are tested in two different laboratories with the same drug, and both laboratories comply with GLPs, that the results will be the same. It is presumed that the GLP structure is being followed by all the major testing laboratories, including those owned and operated by the sponsors of drug themselves.

One of the reasons for the GLP program was a series of incidents during the 1970s in which certain laboratories were shown to have had inadequate controls on the fraudulent activities of their employees. The FDA presumes that the persons who actually did the study are also responsible for the appropriate documentation. Because these persons may be absent from the testing laboratory at a later point when the test substance is being evaluated or challenged, it is essential that they record their data adequately, and that the data be archived or stored in a manner which is appropriate for the FDA to later reconstruct that study.

Audits of the animal data performance by a particular laboratory will often result in findings of minor technical
violations. In some cases the technical violations are easily corrected; in some, changes to satisfy GLPs must be made, and will be followed up by the FDA staff. When a second or subsequent investigation involves the same laboratory, the FDA always checks to determine whether the earlier errors had been corrected appropriately. GLPs give the FDA a structure within which laboratories and the FDA can understand how to achieve the common objective. If the laboratories are not considered to be adequately staffed, or do not install adequate levels of control and documentation, then the FDA can in an extreme case prosecute the laboratory personnel and disqualify the laboratory from being involved in further drug research. If a laboratory is disqualified, that acts as a form of "death penalty". The laboratory cannot be used by companies which wish to get FDA approval of their products. The worst case would be a laboratory which becomes disqualified after a company has invested several hundred thousands of dollars in that laboratory's work on a new chemical. The new chemical then would be pending for IND or NDA clearance. FDA's disqualification means that the laboratory work would have to be done over again in a different laboratory, unless the companies sponsoring the test can show some unusual circumstance (such as an independent outside audit) which makes its particular study valid, even though the laboratory itself was inadequate.
Section 9.6 Assembling the Animal Study Portions of the IND.

An investigational new drug ("IND") application is assembled by the sponsor in a standard format. The transmittal letter should make clear to the FDA medical reviewer that this product is ready to proceed to human testing. The reviewer has inherent skepticism; he or she has probably seen hundreds of similar Phase I products fail in their human studies. The reviewer will be skeptical of the human safety and effectiveness, unless the animal data is clear and clearly expressed. If the animal studies have major flaws, then the FDA might refuse to allow human studies to be conducted in that product. The firm sponsoring the animal studies would be told to repeat those studies or to begin additional major efforts before any human trials in the drug could begin.

The FDA reviewer should be convinced that the animal data has answered the principal questions about human safety. The animal study portion of the IND must be clearly explained. The IND format regulation requires the sponsor to have a full set of animal data; to develop a bibliography of the literature about the drug; to put forth the chemistry and manufacturing data in clear sub-segments; and to provide any information about other drugs which have been made with this active ingredient or this set of components in the past. The AIDS drug's IND, therefore, is going to be built upon the foundation of its animal data. If this important basis is flawed, and the animal data was not adequately
done, then the manufacturer or sponsor may never get the potential new AIDS drug into human studies.

Section 9.7 Why Drugs are Abandoned at this Stage

The typical reason for abandoning a drug at the stage of animal studies is a finding that the drug is too toxic to be tolerated by humans. More development chemistry along this type of products may need to be done, seeking alternatives. But the levels of use in animals may be indicative that the category of products is exceedingly harmful to people. An example might be an anti-viral product which has major impact against the AIDS virus in the bloodstream, but also eliminates many of the blood's white corpuscles. These animal studies might indicate that the drug is too toxic to be tolerated, and therefore the research project would be put on the shelf.

Animal studies might also indicate that the animal model which was selected, often after careful examination of human and animal physiology, did not receive any expected benefits in the bloodstream or target organ from the ingestion of this product. If the product does not affect the animal in the desired or expected manner, then it may not have the desired effects in humans. The projection of human effects from animal studies is always uncertain, but even more so when animals do not naturally have the particular infection. The fight against the AIDS disease is so critical that if the animals show no benefits, the human risks may be too high. Then, any investment in a future human
development becomes less likely, and the sponsor may move on to its next candidate chemical for a possible test drug.

A distinction between mainstream pharmaceutical research and AIDS-related research should be noted. Typically, economic decisions to abandon testing at this point are made early and easily. The additional investment in another cough control product or another wound cleaning agent is not likely if there is a negative aspect to the animal results. Confidentiality of proprietary private research is a method of protecting the investment. Therefore, test sponsors will not tell other companies of the "blind alley" they found and the FDA cannot disclose the failed IND work unless the IND is officially abandoned or unless the sponsoring company consents. In the case of AIDS, both the National Institutes of Health and the Centers for Disease Control actively share data, and companies tend to press forward with AIDS drugs for the potential benefits of studies more than they might for other types of drug uses. Once an AIDS drug development project is abandoned, it is much more likely that these "blind alleys" will be known to all federal researchers and will not be pursued by subsequent developers.

Drugs may also be abandoned at this stage because the pharmaceutical company or other drug sponsor typically has other chemicals that are being tested at the same time. If ten chemicals come out of the animal study phase at roughly the same time, one of the studied drugs may be appropriate to pursue, two might show promise and seven might be insufficiently attractive. The drug
company may invest all of its money on the first drug and leave the other two with some potential untested, because of the high cost of pursuing findings into human research. The decision to test one of three or of ten chemicals, then, is an economic decision. Although animal studies might prove that the product has some attractiveness for later research the drug may be abandoned at this stage by its sponsoring developer because it is not as attractive as one of the alternative products which are in the same "stable" of pharmacological entities.

There is usually no means by which persons who are not directly involved can learn of the past test. It is not published, and except by licensing a set of technology, these nonmanufacturing sponsors do not tell others (including governmental agencies) that such secrets (e.g., failed test results) exist. So redundant testing must be conducted.

Also, a drug might be abandoned at this stage because the drug sponsor finds that the animal studies were not conducted appropriately. Reproducing the animal study in a new laboratory with a new set of animals with a new draft of a new protocol might cost several hundred thousand dollars more than the original investment. Delayed product sale is another cost element. A drug might be abandoned at this stage simply because the cost of any further investment in the drug or the repetition of the failed study will be considered too great.
Section 9.8 The Future of Animal Research

It is possible that, given the amount of effort devoted to AIDS drugs, we may at some time in the future find an animal model which is so easy to use that few animals are needed to determine the potential clinical efficacy of a product. Substituting animals for healthy humans is an appropriate ethical way of screening new drugs. It may also be the case, that valid in vitro tests can be used in the future, in substitution for actual animal or human studies, to do some preliminary screening of the products available for AIDS. It would be better use of the limited number of available primate animals, for example, if science were to develop a screening method for new drugs dependent solely on either laboratory rodents or test-tube bio-engineered microbial products. The likelihood is that animal studies will continue to be necessary, and indeed indispensable, in producing the appropriate predicate and precondition for human studies of potential AIDS-related drugs. One of the benefits of this research on AIDS might be the development of better animal models that can be used for all types of drugs in the future. It is simply too early to tell.
Chapter 10
The Investigational New Drug Process

Section 10.1 When Investigation Approval Is Needed

The investigational new drug ("IND") exemption is an FDA requirement for the limited distribution of an experimental AIDS drug which is both "new" under the law, and not yet approved by the FDA. Drugs are regulated in three categories: "old drugs," "new drugs" which have an approved new drug application; and drugs which are subject to "new drug" approval in the future, but which at the present have an investigational new drug exemption allowing distribution during their period of research and testing. This chapter focuses on the latter category.

Not all tests of drug products require INDs. A marketed drug which is being used for a marketed indication (e.g, toothpaste being sold for dentifrice use) can be evaluated while it is on the market as a means of getting useful information. Typically, the sponsor of the drug needs to find out the experience of the users of that drug and what improvements the users would like to have made in it. The product might also be evaluated several years after its human clinical studies to find out if the product is still having the same level of effectiveness, or perhaps is showing more benefits than it had at the time of the approval. When the marketed drug is tested for its marketed indications, no IND is
necessary because there is no research activity other than the normal use of the normally available product. If a marketed drug is tested for a new indication, which the FDA has not approved in the past, then it would probably require an investigational new drug application for the distribution of the product. For example, aspirin is a "old drug". Aspirin is already marketed, and can be tested for its normal headache or fever indications by anyone who wishes to do so, including the drug's sponsor. But if the sponsor were to distribute 1,000 packages of aspirin marked "new specially buffered for HIV infected persons" and were to distribute these packages to 100 physicians for research on human aspirin consumption among HIV patients, there would be a significant probability that the FDA would treat this item as an unapproved new drug. The change in indications (e.g., to include treatment for AIDS) is a tempting marketing opportunity for unscrupulous manufacturers. Although marketed drugs can be tested for their marketed indication, if the pharmaceutical sponsor wishes to try out an existing drug for an AIDS purpose, it must do so under an IND.

The typical way of determining new indications of a product is to watch both the medical literature and the prescribing trends. Pharmaceutical manufacturers interview physicians and pharmacists to find what kinds of patients are actually receiving the drug, once it is out on the market for sale. By developing information about successful individual physician uses, prescribing that drug for a different indication, the manufacturer determines
where to target its next desired indication or the next desired label change. The manufacturer could then develop research findings which show the effectiveness of the product for that particular medical use.

When the drug developer is researching the new indications which might be developed for an old drug, this phase of research is typically divided into an overview stage, and later the development of a specific IND for the supplementation of an existing drug approval. The manufacturer first determines in an overview of the known existing uses of the drug, what the indications are that are permissible. Next, the manufacturer attempts to specifically develop preclinical and clinical studies which can be run through the IND process to supplement the available claims for the new drug approved-product. The new drug approved-product has a certain set of indications on its label; supplementing these indications requires additional clinical and non-clinical research and studies, leading to FDA approval.

Of course, some studies of over-the-counter drugs are added to, developed, or supplemented on a frequent basis because of the need for advertising substantiation as new claims of effectiveness are developed. These over-the-counter drug products are subject to the continuing supervision of the Federal Trade Commission ("FTC") for their advertising, and therefore the FDA and FTC together would be potential challengers of any excessive advertising claims. Thus an old drug which is sold over the counter could not suddenly make a claim related to HIV infection
without incurring problems from both the FDA (which would treat it as a new drug) and the FTC (which might treat it as misleading drug advertising). The misleading and unapproved drug problems would be dealt with appropriately if the manufacturer had obtained an IND and was following limited clinical testing practices in order to obtain the new information.

Therefore, even though a product may be an old drug, well-known and well established, and even though the old drug might be administered by an individual physician for particular HIV-related uses, to the extent that the drug's sponsor wants to make claims of benefit for HIV infected persons, the IND sponsor would need to develop and submit an IND for the new indications for which the testing is directed.

Section 10.2 Contents of the IND

The format of the IND is specified by regulations of the Food and Drug Administration. All IND submissions must be alike, though certainly the products to which they relate would all be different. Following the FDA format is essential to obtaining rapid clearance of the applications; a confusing or poorly-formatted regulatory submission will not get considered, but will be sent back as incomplete or inappropriate. FDA requires the use of the special form (form FD-1571) which specifies in detail the organization to be used when the sponsor is bringing together its study. Among the documents which should be included in the IND is a list of the ingredients in the drug; a detailed chemical name and
structure describing the chemistry of the drug; formulation and source data concerning the drug; manufacturing methods and quality control information; any information about other clinical work or marketing experience in other countries; and extensive information regarding the preclinical studies which have been performed in animals on this particular chemical. That set of information, while voluminous, is only the beginning.

The essence of a successful IND is the information concerning the intended human clinical study. This information includes the protocol for the study, information about the clinic and the clinic investigator, information about the institutional review board ("IRB") review of the study, and other information about how the rights of patients will be protected. Among the most legally important documents to be attached to the IND submission is the form in which the clinical investigator agrees to be formally bound by the requirements of the FDA regulations which impact on human clinical trials. This is legally important because the clinical investigator is tied by contract into legal obligations which normal physician-patient relations do not produce. The physician who is acting as an clinical investigator takes on an important role in the FDA drug approval process.

The clinical investigator agreements provided for in the FDA's regulations on IND submissions tie in the clinical investigator in a way which makes it possible for the FDA to prosecute such a person in the event of illegal activity. For example, a physician who administers a drug to his or her patient
is generally not liable under the Food, Drug and Cosmetic Act for administering the product at a different dose or for a different indication than the law and the product labeling would require. As a clinical investigator, however, that physician will have signed a contract agreeing to perform the task under the clinical test protocol which has been cleared by the FDA. A test institution, organization, or investigator that signs the document becomes subject to civil or criminal enforcement action by the FDA in the event that the clinical trial requirements are not adequately followed, and as a result of this negligent or conscious action, misleading reports are submitted to the FDA.

In practice, the first principle for the IND sponsor is to protect the clinical patient's rights. The rights of the patient are to be protected from unreasonable risk. Methods of protecting these rights involve a well-prepared investigational plan, and an adequate set of animal data predicting what the safety of the drug will be in humans. The full cooperation of the clinical investigator is essential. The clinical investigator, who provides the informed consent documents and oral briefing to the patient, is extremely important to the protection of the patients. Weaknesses at this point in the process diminish that study's credibility. Drug testing which does not protect test patients may be invalidated.

Among the segments of the IND which are most closely examined by the FDA medical officers, the descriptions of the proposed clinical trials are perhaps the most important. The
trials must be described, the protocols and designs explained, and the source and number of patients detailed. The FDA action on the next phase of product approval is a medical officer's decision, which will be taken on the basis of the case histories of the drug's experience in individual patients. The compilations of case data "make or break" the approval of the next phase. Therefore, it is essential that the data at each stage of process be fully documented, and comport with the terms cleared by the FDA for protocol.

In the case of a product which is being brought to the United States for the first time (e.g., one that is on the market in other countries), the IND should contain complete information about the market experience with that drug in the other nations. If there is extensive experience with a product, or if some of the clinical studies have already been performed inside of the United States, the FDA will be very curious to review that history and will expect a great deal of detail in the IND submission.

The qualifications of the test clinic and of the study investigator should be detailed in the IND. A recurring question is whether the FDA specifies sizes of tests or specific levels of sophistication of the test institution. The FDA's expectations will depend upon the circumstances of the particular drug, and the attitudes of the particular FDA reviewing division. In general, however, adequate experience and adequate staffing to conduct a large scale human clinical study will be essential. The product chemistry and composition information, along with the manufacturing
details, may be of importance, but the central weight and most frequent scrutiny are given to the product experience under the product testing protocol.

In recent years, the amount of attention focused on investigator competence, institutional review boards and informed consent has increased. It is essential that the sponsor of the IND develop information for the FDA regarding the qualifications of the investigator. These credentials should be solid, but in some cases it is not the named investigator who is doing the primary work. If the primary work is being done by another physician, who is not going to sign the protocol, the second physician should be added to the protocol as a co-investigator. The responsibility for the conduct of the study will remain with the primary investigator, but FDA would expect that the second and most active participant be fully identified and be qualified for his or her tasks in the study.

In the case of the AIDS drugs, the attention which FDA pays to clinical tests of the AIDS drugs is intense. Because the agency will pay close attention to these details, it is essential that the drug developer tailor the protocol design to the accurate collection of information from the clinical studies, and particularly to reflect any foreign market experience with these drug. The world wide effort to discover an appropriate AIDS treatment will undoubtedly produce situations in which products are marketed fully (or very extensively tested) in nations other than the United States. It is of great concern to the FDA that adequate
data has been collected from the other nations. Once the FDA sees that a product has been on the market in another country, it may require the detailed examination of that data prior to the approval of the IND. In order to expedite any AIDS drug, for example, FDA management personnel may also contact their counterparts in other national drug regulatory programs to determine whether that other nation had any difficulties experienced after the marketing of the AIDS-related product was permitted.

If the product's sponsor wishes to charge patients for the medication, even though they are volunteers participating in the study, the FDA expects that there will be an explanation in the IND of why it is necessary to make such charges. Typically, the test products are given free; this norm is able to be avoided if the cost of product creation is so large, and the likelihood of this product's approval for treatment of a catastrophic disease such as AIDS is high. It would be worthwhile to read the section of the preamble to the FDA investigational new drug exemption regulations (issued in 1987). It shows that FDA will be skeptical of drug sponsors' charging patients who are part of the drug clinical study.

Section 10.3 The Clinical Hold

The 1962 New Drug Amendments, which established the IND process in such great detail, did not provide for the FDA to specifically approve each drug test in advance. Rather, the FDA was given authority to stop the drug from being administered to
patients, if the FDA felt that questions about the test drug were not adequately answered by the papers submitted. The FDA asks these questions in the form of telephone calls and follow-up written communications. These communications inform the sponsor that there is a "clinical hold" on the IND. This means that FDA, using its authority under the law, declines to permit the clinical testing of the drug to proceed. This is not the same as denying an approval; the statutory system for INDs is not one of approval, but one of "negative option." If the FDA does not act, does not take up the option to stop a test, then it would go forward. FDA uses these clinical hold devices in order to restrain human exposure to products until and unless the FDA is satisfied that the manufacturer and sponsor have thoroughly considered, and are ready with answers to the types of questions which are of greatest interest to the FDA medical officer/reviewer.

The clinical hold is usually in place for a limited period of time, after the FDA has obtained the responses from the company. However, it is prudent to recognize that subsequent clinical holds are not unknown. FDA may respond to the company's initial response with yet another set of questions concerning the IND. FDA might do this by telephone on the 28th day, spoiling the expected 30-day approval clock. Because it is a matter of statutory authority for the FDA to intercede to stop a drug's use in clinical patients, there is probably no appeal. Therefore, the company interested in the IND has very little leverage. The company could ask higher-level FDA officials to lift the temporary
"hold," but this is unlikely to be successful. Fighting the FDA over the terms of a clinical hold virtually never happens, because the FDA's discretion is so broad in this area. A court would not overrule the FDA if the FDA declines to allow the IND exemption to apply to a particular drug.

Section 10.4 Participants in the Testing

The process of getting an AIDS drug to the market will require support of several types of professionals, and many non-professionals' support as well. Perhaps the commonplace myth that FDA itself tests all drugs makes it difficult to educate the public about why AIDS drug development must involve so many individuals from so many areas.

The most important actors are the investigators. These are the physicians, supported by staff nurses and other medical personnel who actually administer the drug to the test subject patient, and record the body's reaction to the drug product. It is very important that a drug sponsor have a credible, competent investigator. The inadequacies of an investigator may prevent a drug from reaching the market, because the FDA in a subsequent audit of the work done by the investigator may not be able to reconstruct the factual evidence gathered by that person. FDA would reject the results of the clinical research if not documented properly.

The physician-investigator typically involves in the research a co-investigator and several support persons who have
clinical experience in the hospital or institution within which the research is being done. For example, if clinical research is being done within a health maintenance organization clinic, several of the clinic's nurses and administrative support staff will be part of the clinical investigation team. The investigator, however, must be accountable. He or she must be individually well-qualified and well-prepared to undertake the record-keeping and monitoring functions, and to assure that patient care will not suffer during the fact-gathering portion of the clinical study. It is the responsibility of the investigator to be cautious of the needs of the individual patients, as well as of the need for scientifically unbiased study results. Because the investigator must serve two responsibilities, those to the patient and those to the drug sponsor, the responsibility of pharmaceutical investigations can be quite difficult for the inexperienced physician. For that reason, investigators typically have considerable experience, and work as a team with other co-investigators to develop their medical research results. Medical clinical trial work is a task learned from experience.

A well-trained support staff, especially of nurses, is extremely important to proper documentation of the research data. Although the physician-investigator is contractually responsible for the accuracy of the study data, the actual questionnaires and documentation of patient qualification are kept by the nurses. The nurse or physician assistant produces the records, provides the dose of drug to the patient, questions the patient at each visit
to the clinic and generally keeps the paper work flowing. The investigator has the responsibility to oversee this work. In the best clinical studies, close cooperation between nurse, physician, and physician's assistant makes the clinical study team very effective.

The institution in which the clinical research is conducted must have an adequate patient "pool" from which to draw in Phase II and Phase III studies. In each of these phases, the institution is taking patients who are being treated for that illness and recruiting them to participate in an experimental therapy. Although some institutions welcome the opportunity to do clinical research because of the additional income which the sponsor can provide, some institutions are hesitant to take on costs over and above Medicare/Medicaid or insurance coverage of the individual patients who may be treated for that condition. The institution, usually represented by a coordinator of research, verifies the adequacy of the research before the projects are initiated at their institution and a contract for reimbursement of costs (plus overhead) is prepared.

The institutional review board, discussed in greater detail in Chapter 7, is an important part of the institution's clearance of the drug study. Clinical drug patients should expect that the institutional review board will have examined the safety aspects of the drugs and the ethical aspects of the study design before placing the study in that institution.
The sponsor of the drug is the manufacturer or U.S. agent of the manufacturer. Typically, the sponsor is a pharmaceutical manufacturing organization. The sponsor has developed the drug or developed data concerning a licensing company's drug, and has filed the investigational drug exemption application (IND) with the FDA. The sponsor is responsible to the FDA for any deficiencies in the data developed concerning its product. If a product is not adequately tested, the sponsor bears product liability risks, potential criminal liability as well as responsibility to the FDA for such inadequacies. The economic incentive for doing clinical research, of course, is that if the sponsor completes the research in an adequate manner and an adequate time, the product may well be approved by the FDA prior to the approval of competing products which are sponsored by competitors. The sponsor therefore wants maximum FDA acceptability for its qualities of research.

The sponsoring organization generally hires a monitor, who is a research professional familiar with the documentation and conduct of such clinical studies. This monitor is responsible for making sure that the documentation will be adequate at the time that it is submitted to the Food and Drug Administration. This monitor is also responsible to the company to make sure that it is receiving its money's worth of research services from the clinical physician. If the clinical physician is not providing the service, then both the company and the FDA are being deceived. A monitor should catch any situation of fraud, but more frequently will catch any serious deficiency in the system which unintentionally is
making the research information less valuable. Therefore, a good monitor will understand the systems which should be in place, and will compel the investigator to cleanup its faulty procedures.

The sponsor typically will have a quality control unit to which this monitor reports, which can provide assistance to an investigator who is developing problems. Clinical research quality control functions include the auditing of the adequacy of patient records, informed consent, dosing information, study controls (number and name of the drugs being administered), and other information. Because this research investment is often in the hundred of thousands of dollars, sponsors have many economic incentives to assure that adequate investigatory research is actually being done with the sponsor's money by the investigator.

Certainly the most basic ingredients are the patients or test subjects. In Phase I, test subjects are not ill; there are usually college students or unemployed persons who are given a reasonable amount of money for a week or two weeks of medical tests during isolation at a clinical research site. This isolation, and the blood tests which are given to determine the safety of doses of the drug, is an important step in the drug development process. The actual recipient of these experimental drugs, who has qualified to receive the drug under the Phase I protocol, is likely to be a person who has both the good health and the time needed to participate in such a study.
The test subjects who are of greatest interest to FDA are HIV-infected persons who voluntarily participate in Phases II and III. There is much more pressure for persons with HIV infection to become a part of the study. The system of testing does not encourage large-size study distribution. A drug sponsor probably does not have economic incentives to bring all of those wishing to be part of the study into the research group. Rather, there may be compassionate reasons why the investigational drugs should be administered to these persons. The test patients should be physically capable of producing clinical results which will not be complicated by the effects of other medications. A test subject who is on other medication may complicate the results of the experiment because of results attributable to the non-test drug(s), and therefore should be excluded.

In the case of HIV-infected persons, because so many persons are seeking a cure for a serious illness, the investigator and the sponsor's representative should make certain that the clinical patients understand how important it is that they NOT take other AIDS drug while the primary investigational product is being consumed. This is essential to the accuracy of the test results. Getting patients to comply with the dosing required in the study; dealing with those patients who wish to drop out; and adequately recording the information about patients who show varying degrees of cooperation, are among the problems experienced by clinical investigators. Because these are human, rather than animal or laboratory, studies, the FDA recognizes that there may be variable
factors related to patient compliance and patient cooperation. However, the FDA insists that the work done for a medical research purpose must be done in adequate and appropriate manner. For any particular test, the terms "adequate" and "appropriate" will be defined later by the FDA in hindsight.

Section 10.5 - Role of FDA during the Clinical Investigation Phase

FDA typically meets with the sponsoring company several times during the pharmaceutical drug or vaccine development. In the case of a vaccine, FDA scientists are likely to be actively involved in product research and testing. In the case of a pharmaceutical drug, the FDA scientists review the documentation offered and the rationale for it, but reviewers rarely have hands-on experience with that type of drug in that type of patient. Presentations by sponsors are a principal source of insights as well as data. The FDA meetings are much more formalized and stylized as to format. The FDA insists that the manufacturer request the meeting with a detailed agenda of the points on which the FDA and the manufacturer should agree. The FDA considers these detailed submissions before deciding whether there should be a meeting at all. If there is a meeting at the end of Phase I studies (and the new NDA "fast track" regulations seem to strongly suggest that meetings would be appropriate), then the FDA has an important opportunity to shape the future of the medical research program.
Meetings with FDA to discuss a clinical test protocol generally require advance submission of the document which will be the subject of the decisions to be made at the meeting. The FDA expects the company will make a submission, the FDA will make comments on the submission, and the comments will then be accepted by the company. From the government's perspective, these suggestions should be presumed to be both authoritative and persuasive.

However, most companies come to this protocol review task from a different direction. The private sector research scientists view themselves as extremely well qualified to create an appropriate clinical study protocol. If the FDA does not defer to this view, and frequently FDA will not, then the best route for the manufacturer or sponsor would be to bring in an outside consultant who is familiar with both this type of drug and the operation of the FDA. Such an outside person could intercede with the FDA and develop a process of accommodating FDA's concerns about the drug.

Whether a sponsor is a winner or loser after meeting with the FDA is often hard to determine. Some meetings generally produce agreement on the next phase of protocol development, and smooth the way for rapid approval. For "fast track" AIDS drugs, companies try to get FDA's written agreement to approve a particular test method, size and site. In the case of AIDS drugs, investigators and sponsors may be able to persuade the FDA personnel in personal meetings to the benefits of a particular
protocol condition which would on paper appear unreasonable. AIDS drugs may merit special control methods or special patient-eligibility criteria.

When meetings are appropriately prepared and handled, they can be extremely effective toward getting the advance agreement of the medical officer for the later stage of approval of the NDA in this product category. Because the same medical officer will be involved at the IND and NDA stages, in many cases, the time spent on IND meetings will build a strong relationship of trust and mutual respect, resulting in time well spent. If a change of personnel occurs, much re-learning will inevitably occur, delaying the NDA, and requiring more sponsor explanations.

Section 10.6 Foreign Experience with Drugs To Be Tested in the U.S.

The IND application sent to the FDA requires the sponsor to disclose any actual clinical experiences developed in foreign countries, whether through foreign clinical experiments or by marketing its product in the normal marketplace. This foreign experience data can be an important source of persuasion to the FDA that the product has been adequately tested. For example, in the case of the drug Lovastatin, the Phase I studies were done outside the United States, and the United States was the site of Phase II studies. Typically, however, the foreign clinical test standards are not as rigorous as those imposed by the FDA. Therefore, foreign clinical studies will require additional supplementary data.
developed within the United States and in compliance with FDA requirements.

FDA finds it very useful to have foreign clinical experience and information, so that it can rule out questions concerning the possible activity of the drug in marketplace situations, where the controls are less stringent than they might be in clinical experimentation. It would be ideal if every drug test produced results which perfectly predict future marketplace results. However, many drug tests produce mixed results. In these circumstances, the statistics on marketed drug experience under foreign approval systems will assist the FDA. It will often give credence to the sponsor's assertion that the drug would be safe and effective in its future market experience.

In rare cases, the FDA goes further. In the case of heart attack control drug, Propolanol, the FDA accepted a single large scale Norwegian clinical study as a sufficient basis for U.S. approval. This is a rare event; the FDA often insists that the quality of scientific research in human pharmaceuticals is much lower in many other countries than it is in the United States. The Congress accepted this presumption in the Drug Export Act in 1986.

When this FDA approach of favoring U.S.-developed data is examined closely, it is often true that the foreign clinical studies produced adequate and reasonable scientific evidence. It is also often true that the paperwork requirements of the FDA in the United States are not fully met by the clinical study practices.
of foreign institutions. The FDA, with its insistence upon elaborate documentation, generally favors U.S.-generated clinical data over that generated in foreign clinical sites.

An additional factor discouraging FDA from ready acceptance of foreign clinical work is that the FDA does not have a large enough budget to conduct exhaustive on-site audits of clinical work conducted in foreign countries. If the FDA had such additional auditing capabilities, with a larger travel and expense budget, it is more likely that the foreign studies would be given credence. FDA is not able to get to the Norwegian, Swiss or Chinese sites of the clinical experimentation and therefore, the studies may need to be duplicated within the United States, at a significant increase in costs and time of approval.

This same situation had been resolved in the nations of the European Community through the dossier system of approval, in which one country's approval of the drug generally was adequate for the approval of the drug in other nations without repeating each clinical study in each country. The FDA may reach this point of acceptance of other nations' clinical studies in the future, but at present, the FDA requires U.S.-based clinical studies in virtually all cases of drug approval. Without that data, the FDA does not accept the adequacy of the research to show the effectiveness of the particular drug.

In the case of a product intended for use against HIV infection, work being done currently in Africa, among populations of heterosexual, HIV-infected persons may be extremely important.
However, because the lesser developed countries in which AIDS is a problem may not have the same level of cautious medical research, medical experimentation and ethical protection of patients which the FDA expects to find in the United States, the FDA may be biased against the acceptance of that data. Therefore, while foreign clinical tests of AIDS treatment drugs are helpful, they are not perceived as a body of information which can be used efficiently in support of a rapid FDA approval of a human drug for use in this country. Whether that perception is a result of "imperialism" in the disregard of foreign clinical investigations' adequacy, or whether it is a case of bureaucratic excess caution, clearly part of U.S. approval does require U.S.-based tests. The FDA practice of using foreign clinical data will undoubtedly expand as the result of the difficulty of getting adequate information concerning AIDS-related drugs.

For the long term, foreign clinical work with new therapeutic entities against AIDS will push the institutional limits of the FDA system. Need and public demand for AIDS-related drug products will actively promote the acceptance by the FDA of foreign clinical results in HIV-infected persons regardless of their national origin or clinical site. There will also be political pressure for the FDA to grant faster approval to those products which are already on the market and which already appear to be working in sophisticated foreign countries.

Although the FDA recognizes foreign market experience as one source of IND drug supporting data, FDA is generally reluctant
to reward faster drug approval even in the face of news that another nation has granted approval for marketing of that product. The FDA generally takes the attitude that U.S. approval conditions are the toughest in the world, and that U.S. consumers are the best protected in the world. To open up the pipeline and change that attitude, researchers working on AIDS drugs should keep in mind that they need to persuade the FDA to accept the adequacy of foreign clinical data, and they simultaneously need to raise the quality level and reproducibility level of foreign clinical data, to the point that such data is much more readily accepted by United States' FDA officials. In some cases, this may mean going so far as to demand that the foreign institutions set up institutional review boards, patient informed consent procedures, and drug accountability programs that may not now exist in a given nation's practice of drug approval and licensing. Achieving this change in attitudes in the foreign nation may bring their research work closer to the attitudinal expectations of the FDA medical officers. If the studies can be published in U.S. clinical testing journals as well, that measure of peer group acceptance adds additional support for the thesis that the drug testing work is adequate in that other nation.
CHAPTER 11

How Clinical Trials Are Conducted in Humans

Section 11.1 What is a "Study"

The 1962 law which governs products intended for the treatment of AIDS and other diseases requires the FDA to examine adequate and well controlled "studies." It is important to remember that FDA does not do the studies. Rather, FDA-reviewed medical research is done at hospitals and other research institutions. That research produces data that is organized into a package with supporting documents, all of which collectively is known as a "study."

The study definition in the statute appears to the FDA (and to the judiciary) to exclude anecdotal or episodic information obtained by a drug sponsor, including results from miscellaneous clinical uses of the drug by individual physicians. It is not sufficient to constitute a "study" from the experience or observations of even the finest physician researchers. Formal, planned observation is mandatory. A study requires a defined research goal, a defined set of patients, a defined protocol or method of operation and a defined dosage of the drug product. The study is then conducted in the volunteer patients after informing them of the risks and seeking their consent. The study is
documented, and a final report of the study is written by the sponsor's technical staff, and then reviewed and signed by the clinical investigator who is responsible for the administration of the drug to patients.

The "study" definition may be used regardless of size of the studied population. A Phase III clinical test which measures drug effectiveness in a multi-center trial may enroll 800 patients, while a rare disease may be detected and a drug may be tested among only 20 volunteers. It is the method, not the studied population size, which counts.

Section 11.2 Types of Controls Found in Clinical Studies

The purpose of a control in a human clinical study is to produce a reproducible effect, with limitation of the bias toward effectiveness that often can be encountered in the course of a human clinical study. Biases include excessive selection of a particular class of patients, in a way which produces one particular outcome. Bias is also included in the selection of patients from one particular group that is not representative of the types of persons who will actually be served by the drug after product approval. Effectiveness in a very small and isolated subgroup of the population may not indicate that the same quality of benefit will be experienced by others. An unbiased study seeks the same level of attention to the dosing of this drug in the small tested population as in the public at large. Bias, whether consciously or unconsciously present in the test, will need to be
defended when FDA's biostatisticians review the study months (or even years) after patients complete the study.

"Blinding" conceals information about the identity of the actual product which the patient consumes during the study. The control of the information available to the patient and to the investigator is intended to avoid biases such as the patient anticipating physical benefit, and thus experiencing a psychological benefit, of knowing that he or she is actually receiving the active drug. The patient may have a psychological barrier to reporting a benefit, if the patient believes he or she are not receiving the actual drug. Conversely, the patient may have an appropriate expectation of benefit, and some physiological benefit can be claimed, if the patient is actually able to determine that he or she is receiving the drug. For example, if a drug turns the patient's skin yellow when topically applied, then the placebo drug must do the same. If the placebo does not do the same, then the patient will be able to determine that he or she is receiving the placebo. There may be some psychological impact on the attitude of the patient toward the therapeutic program, which reduces the all-important "compliance" or patient obedience to the rules of the study group.

The placebo control issue is a controversial one. Placebo control studies are those in which the active drug product is given to some patients, while other patients receive only a sugar pill (e.g., placebo) with no active ingredient. Both the sugar pill and the active product are made to look identical.
placebo effect is the psychological improvement a patient may show when believing that he or she is actually receiving an active drug product, as discussed above. This placebo effect is normal and anticipated, including some psychological improvement in the attitude of the patient toward the disease. Some studies could have three "legs," composed of groups of patients who receive the new AIDS drug; others who receive ACT; and some who receive the placebo. The more serious the disease, including catastrophic illnesses like AIDS, then the more important it will be to avoid the occurrence of a misleading placebo effect in the course of the clinical research. For the majority of patients who are not receiving the placebo, but receiving instead the active drug product, there should be measurable medical benefit observed during the course of the patient research.

Well-controlled studies do not always require a placebo, though a placebo test has been described by FDA in an October 1988 press statement as "the fastest way to find out if an experimental drug is effective against a disease with no known cure." The arrival of ACT makes it more ethically and realistically proper to have a control product (e.g., ACT) rather than a mere placebo. The selection of which control method to use has to balance information development objectives of the drug study with ethical standards for patient care.

Some drug tests for life-threatening conditions do not use a placebo control. In these tests, it is deemed unethical to leave patients who have a fatal disease with only a sugar pill.
For these patients, it would be unfair to not provide some measure of effective relief. In the case of an AIDS drug, an active control such as the already-approved ACT drug (zidovudine) may be utilized. The ACT "active control" is an ethical way of conducting human research in a situation in which the patient desperately needs some relief from the illness. In the case of an AIDS vaccine, it will be very difficult to get an appropriate control mechanism, since a vaccine without any efficacy benefit may be difficult to ethically justify as a test substance for the patient population which is being tested.

Section 11.3 The Research Protocol Design

The research protocol is an extremely important part of the clinical trial. It is the road map which is to be followed by the clinical researcher. The use of a protocol is intended to guide the activities of the investigator, leading to the proof or disproof of a hypothesis that the particular drug will produce a medical benefit. If the protocol is adequately designed, then the efficacy question posed by the investigators should be adequately answered. If the clinical study protocol is not adequate, then despite the collection of points of data from individual case reports, the end product of the study may not be scientifically convincing. The study then would be of no particular usefulness in the FDA approval of an AIDS drug or a vaccine. It is essential that the protocol design work be done with care and precision.
The drafters of the research protocol will not be infallible. During the FDA auditing of an on-going clinical study, or at the time of the FDA review of the IND application, it may become clear that there is a need for the protocol to be amended. The protocol for dosing may need to be sharpened, a class of persons may be added or deleted from the protocol-stated qualifications for the drug, or other changes to the protocol may be necessary. An amendment is prepared, stating what the change to the protocol will be. The amendment documents include the signatures of the clinical investigator, the sponsor, and other appropriate officials. That change in product protocol should be documented and kept in the investigator's file for future auditing by the FDA.

Section 11.4 Statistical Success of the Clinical Trial

A clinical trial of drug safety is studied by biostatisticians to determine if adverse reaction rates exceeded expectations. This is done separately from later calculations concerning effectiveness. A clinical trial of drug effectiveness is not a success unless a biostatistician who examines the effectiveness of the drug is satisfied that there is a statistically significant improvement in patient conditions from the administration of this drug. It is important that the statistical significance be established, because otherwise the "scientific control" portion of the medical research requirement would not be met.
Clinical research requires statistical examination of data generated as a result of all the clinical studies. For example, an HIV infected person may have a one in thirty chance of an adverse reaction caused by the taking of a particular AIDS-related drug. The probability of injury from the drug should be thoroughly understood as a result of that clinical study. If it is not well understood, the FDA may hold up the approval of the product and require that the sponsor produce a safer pharmaceutical entity. The larger the number of patients engaged in the clinical research, the more statistical assurance there will be that an isolated adverse reaction in one or two patients will not be representative of the response to the drug among patients at large.

The reason for the statistical precision of analysis during the clinical studies phase is that FDA is very concerned about finding adverse reactions before the product goes into the market place. If the product goes into the market place and does not have adequate testing, FDA may have to later deal with the consequences of unexpected adverse reactions. However, if the statistical work is done to examine results on an adequate numerical base of patients, then the FDA may be able to add as a requirement of approval an adequate set of physician or patient warnings alerting the prescriber and consumers of the drug that a particular kind of injury or illness could develop under certain conditions. The precision and caution used in statistical analysis of a new pharmaceutical product is extremely important.
Perhaps the most difficult chore for the statistician in dealing with clinical trials, is the case of a clinical trial in which an inadequate difference in numbers of patients exists between those who experienced a measurable benefit from the product and those who did not. The adequate and well controlled studies must show a superior outcome of patient benefit, to offset the inevitable risks from ingesting any pharmaceutical drug. Statistically significant differences in the patient benefits of a drug are important to getting that drug's approval through the FDA system. "Effectiveness" is measured by the extent to which a biostatistician can demonstrate from the study data itself that the study supports a statistically significant improvement of patient condition. Patient improvement with the drug, as opposed to patients who did not receive the drug, defines whether there is a net benefit and a rationale justifying the FDA approval of the product.

Section 11.5 Reporting Requirements for Clinical Studies

The medical officers and reviewing officials in the FDA reviewing divisions have examined the IND and have permitted the research to start. They expect to hear reports on a regular basis about how the research is going and what outcomes are likely to occur as a result of the clinical investigation. If appropriate, a successful study will lead to the filing of an IND for further studies or the filing of an NDA for approval of the drug. These medical reviewers in the drug review branches of the FDA are
gatekeepers. The product approval process will hinge upon adequate data being presented to and accepted by them. They will await the outcome of the clinical studies and will await the submission of the finished clinical data in the course of the NDA application, which is to be filed at the end of the IND research process.

However, in the meantime, they also have an interest in making sure that the clinical patients are adequately protected. For that purpose, the FDA requires periodic reports of any adverse reactions which are developed or detected during the clinical research phase. In the case of an AIDS drug, for example, severe physical or neurological effects discovered with this drug during the treatment of HIV-infected persons must be reported promptly to the FDA. The reason for this rapid examination of the experience with the drug is to make certain that adequate information is continually flowing into the FDA during the IND period. If the product is producing a high level of adverse reactions, or much more serious reactions than were expected, then the FDA may step in and require the sponsor to stop further clinical data gathering and further administration of the drug to patients.

During the drug clinical trials, it is mandatory that the adverse drug experiences from both U.S. and foreign sources be promptly disclosed to the FDA. Drug experience data is essential to the FDA's continuing review of the IND products. If there is a very serious and unexpected adverse drug experience with the new product, the FDA must be notified within 15 working days after the initial receipt of the information by the drug company. The FDA
expects that these 15-day reports will be followed up with adequate documentation of what the firm has learned, and the follow-up reports will provide greater detail and information from which an analysis can be made by the FDA. In addition, periodic reviews of the adverse reactions which are serious and expected must be reported to the FDA. Typically, because of some concomitant drug being used or some external factor, the patient suffers an adverse reaction which is not directly caused by the investigational pharmaceutical. The FDA recognizes that not all 15-day alert reports will prove to be factually justified by the concern about the particular drug to which the experimentation is directed. These alert reports are not determinative of any particular FDA action against the product. However, it is very important that the alert reports be done properly and adequately, as soon as the firm learns of the clinical problem, severe adverse reaction, foreign marketed drug reaction, or scientific literature report. Regardless of the source, if the sponsor learns of the serious adverse information, the report of this unanticipated reaction should be filed as soon as possible in order to make certain that the FDA understands the existence of this potential risk factor in the pending IND drug research.

The sponsor must also report to the FDA about the progress of the IND on at least an annual basis. An annual update is needed of the activity under the IND, such as additional subjects enrolled, additional human or non-clinical studies performed, and the like. These reporting requirements are the
principal linkage between the FDA and the day-to-day work of the clinical investigators. Because the FDA gets these periodic reports, it is able to determine whether patients are incurring severe adverse reactions at a rate that is not an acceptable risk. Reports also inform the institution's review board, which might decide to stop further research if the reactions were too extreme or too frequent.

In the case of AIDS and related drugs, the importance attached to reporting requirements is even greater. The FDA is very concerned that the AIDS-related drug products should be monitored closely, and that reports be filed as rapidly as feasible, so that FDA cannot be challenged for inadequately supervising the conduct of clinical trials among these "fast track" drugs. The FDA is aware that it might be charged in the future with a lack of adequate supervision of clinical trials, which if poorly planned or executed could produce significant levels of adverse reactions or death. For that purpose, FDA is fastidious about checking the adverse reactions which are reported with the high-priority, fast-track, AIDS drug products. The FDA is particularly sensitive that clinical patient injuries from administration of an AIDS vaccine may, if not detected and studied early enough, proliferate rapidly. Too many adverse experiences would, in turn, cause adverse publicity about an otherwise effective and needed vaccine. With appropriate reporting levels, the FDA will be able prepared to intervene in the clinical trials if necessary, in order to suspend the use of the drug during its
reformulation. FDA's cooperative efforts with the sponsor may forestall adverse publicity arising out of misunderstandings, which otherwise might damage the future public acceptance of the product.
CHAPTER 12

Safeguards for the Patient

Section 12.1 Informed Consent Policy

The Food and Drug Administration has specific regulations requiring the "informed consent" of a patient before an experimental drug may be administered to that patient. Informed consent must be in writing and must be signed by the investigator and the patient who receives the investigational drug. It is not permissible for the patient to receive the investigational drug before the informed consent is given. But in very unusual cases, a waiver of informed consent may be used for a patient who is unconscious, who is in serious medical jeopardy, and who absolutely needs the drug product in order to avoid a serious or potentially fatal consequence of not receiving the experimental drug product.

FDA informed consent regulations are stringent protections for the rights of the clinical patient. These rights and protective devices are more closely followed in the United States than in many other nations of the world. One reason for that stringency of product clinical testing consent requirement was the result of World War II experiences with German experiments on concentration camp inmates or prisoners. Following these inhumane and often ghoulish experiences of World
War II, the United States and other countries subscribed to the Nuremberg Agreements on medical research. Thereafter, nations agreed to follow requirements for non-coercive informed consent by the patient before the patient is exposed to the drug.

The United States investigational drug system is conditioned upon the drug test subject (e.g., patient) having given adequate and voluntary informed consent. The FDA could refuse to consider a specific clinical research result, forcing a new study, if the product's sponsor had used an inappropriate method of obtaining consent or had obtained no consent at all prior to administering any drug product to the test subject or patient.

The FDA's informed consent policy is carried out through a written contract which is required to be signed by each clinical investigator, who agrees in advance to obtain written informed consent from patient in a study. The FDA implements this rigid standard of conduct through audits of the clinical studies which are submitted to the FDA, and the FDA also uses the leverage of local authority over the sponsor and investigator. FDA requires that informed consent forms be reviewed by the institutional review board of the hospital or clinic in which the investigation is being done. It is very significant that the FDA provides multiple levels of local and Federal review of these informed consent provisions, so that there is no way a clinical investigator for a drug could conduct an experiment in any reputable hospital without being aware of the need for informed consent.

186
Medical experimentation on a unconsenting person could be considered a form of the crime of battery under state criminal laws. But for FDA purposes, regardless of the status of the particular experimentation on the patient, research done without proper informed consent could never be submitted to the FDA for approval of the test product. Informed consent by patients is thus required and inevitable before a new drug is tested.

The content of the informed consent is also specified in FDA regulations. The FDA insists that the informed consent advise the patient of the potential adverse reactions which might occur from the administration of the drug. The sponsor may provide information about the alternative therapies that are available, and should provide some assurance that the sponsor is willing to pay for the test-related medical expenses which might be incurred by the patient, if an adverse reaction should arise during the course of the investigation. Typically, a sponsoring company will provide information about the adverse effects and will provide in the informed consent document a commitment to pay for the reasonable medical expenses of a person who is injured in that experimentation. The details of such agreements vary, of course, from sponsor to sponsor and from institution to institution.

As a basic principle, there must be no coercion of persons to "volunteer" for drug testing. The FDA and a special Presidential Commission which studied clinical testing and informed consent several years ago, specifically disfavored the use of patient populations, such as prisoners and infants or children, as
test subjects in clinical trials. Except where such patients are especially at risk, it may be unethical for research to be done, with their compromised or limited capacity to consent, of these protected classes of persons. The prevalence of AIDS among these populations poses special considerations, which are subject to continuing debate.

Because the informed consent documentation is always requested by the FDA auditor at the time that the auditor reviews a clinical study, it would be unthinkable for a drug product sponsor to conduct an experiment in which patients are exposed to the drug without first obtaining written informed consent.

In summary, informed consent requirements are buttressed by appropriate institutional screening, personal tort liability fears, and common sense. Where it is not properly handled, multiple significant problems can and will arise from the omission of informed consent procedures.

Section 12.2 - Consent Problems with AIDS Drugs

The well-organized and understood principles of informed consent for the use of pharmaceutical products in human medical experiments are scrambled in the context of a fatal disease marked by dramatic anxieties among the potential patient population. There will be no clear cure for AIDS for several years to come. Persons concerned about their status as HIV-infected persons have expressed depression and significant frustration upon examining statistics on life span and the likelihood for the development of
active symptoms. In the case of an AIDS drug, therefore, there are many elements of implied coercion. The coercion is not the result of actions by the drug sponsor, but coercion through reality that they may be no alternative viable medication, other than the one being offered in test, which an HIV-infected person may obtain.

In the case of AIDS drugs, it is essential that the informed consent document be very thoughtfully worded so that the patient does not have unreasonable expectations of results from cooperating with the research project. The research being done may or may not have benefit for the specific individual test subject. Rather, the test may be unsuccessful for that person who takes the drug at that dose, but may be very successful at a higher dose in other patients upon mass marketing. Therefore, the AIDS drug should not be presented with an informed consent document which over-promises or over-creates an expectation of immediate patient benefit.

Patient eligibility criteria are important controls on the adequacy of a drug effectiveness study. In some cases, persons who are, on a medical basis eligible to receive the AIDS drug may not be eligible for a particular study after consideration of all the relevant factors. For example, a person who has developed symptoms of Kaposi's Sarcoma may be taking a large dose of another, as yet unapproved, drug at the time that the person is on the list of potential recipients of the investigated clinical drug alpha interferon. In such a circumstance, the protocol would direct that the person should not receive the AIDS drug as part of the
experimental program, since the results of the experiment would be questioned in light of the concomitant use of an alternative therapeutic product. The results of an AIDS drug study in which 5 or 10 patients were simultaneously taking 1, or 5 or 10 additional drugs, in the belief that those additional drugs would be useful for AIDS, would result in a skewed experimental outcome, invalidating the results of the research.

This problem of other AIDS medications which will complicate the clinical findings of a study is very serious. The factual conclusions to be drawn about particular test patients will be less accurate if their favorable improvement is in part due to a special additional feature not shared by others in the study or control groups. For example, a serious threat to immunocompromised persons is pneumocystitis carinii pneumonia. The pneumonia is not a high risk for patients who are not yet seriously affected by HIV's compromising of the immune system. So, as FDA urged in an October 1988 press statement, testing of drugs against this kind of pneumonia should be done without complication by the use of incidental extra therapies during the study period.

Part of the informed consent process should be an identification of the ability of each patient to adhere to the terms of participation in the study. However, a particular patient may be so concerned about his or her state of illness that the option of full compliance with the drug testing requirements is not as "pure" an option as it would be in the standard norm of testing for traditional drugs for traditional diseases.
An important criterion of a truthful informed consent document is that the patient not be promised a level of effectiveness which the drug cannot deliver. The patient should be informed that the investigator does not know what the net benefit of the product will be for his or her particular state of health. Indeed, in many clinical experiments, there are some patients who have an early reaction to the drug who are removed from the study population rather than risk a worsened side effect. For these patients, there will be no benefit at all from participation in the study. In the case of the AIDS drugs, for example, the manufacturer cannot promise that the HIV virus and its symptomatic consequences will be stopped by the effects of the particular vaccine or drug. Rather, the manufacturer can give details of the early animal experimentation and suggest how the product may work within the body. The manufacturer cannot go farther to promise the patient that the drug will produce any "guaranteed" benefit for an individual patient.

Nonetheless, when a product is available for the treatment of a serious and often fatal disease, patients will make the decision for themselves that they will take the medication as part of the experimental group rather than be foreclosed from taking it because of its lack of assured results. In light of the well-understood odds for HIV-infected persons, the benefits of experimental drug tests exceed normal benefit ratios for clinical drug tests.
Because the AIDS drug informed consent issue is such a controversial one, it is likely that litigation over the adequacy of disclosure in the informed consent documents will arise in the future. Of particular concern to developers of vaccines is the use of the AIDS vaccine in Phase I clinical studies. During the Phase I study, the product is tested in healthy volunteers rather than in persons who have already developed the disease. For these persons who are healthy, taking a vaccine which may produce a body's natural defense antibodies against the HIV virus may have an unusual side effect. The person may, following the taking of the experimental vaccine, show medical test results in the future which suggest that the person has AIDS. The medical tests done on blood demonstrate the presence of certain antibodies; typically, these antibodies are present in a person who has the illness. But if the person does not have the illness and takes the experimental vaccine, he or she later may be found to have the antibody, and anyone interested in the person's AIDS-related status may later incorrectly conclude that the test subject himself or herself has an active HIV infection. More sophisticated tests using genetic materials can differentiate among the HIV-related blood components. But the potential error with the basic screening tests is a problem for test subjects.

Part of the informed consent for Phase I clinical trials of AIDS vaccines will be to explain the potential social and occupational negative results which could affect a volunteer who participates in such an antibody-generating medical study. The law
does not deal with this potential harm, because it is so unpredictable in consequences; it does, however, require that there be full and fair explanation of the consequences to the person who volunteer to take the drug. In vaccine studies, consent documents would also describe a remote possibility of vaccine-induced infection.

In the case of the AIDS vaccines, therefore, it may be difficult to obtain a full cohort of healthy persons willing to voluntarily accept the risk of AIDS related discrimination in the future, as the result of their free participation in such studies of vaccine development. It may be appropriate for the vaccine developer to provide some form of identification of such patients so that the persons can disclose this experimental exposure to HIV-related antibodies in the event of a future question about their screening test results.

An additional special problem of informed consent for AIDS drugs is the existence of an alternative therapy. When an alternative therapy exists, there is an ethical question about whether the informed consent has properly told the patient that there is another drug available, other than the investigational product, which may have a beneficial effect. The consequences of making this disclosure might be to lessen the interest of infected persons in taking the particular experimental drug. For example, the person already knowing that he or she is HIV-infected may know that instead of experimental drug A, they could be helped by the marketed drug AZT. The person giving the informed consent to
participate in the study of the drug A is therefore made aware that instead of the uncertainty of drug A, he or she may obtain a more certain outcome from taking the existing product. Participation should be encouraged; it is important that the experimentation go forward so that AZT and products which come after it may all be available for the treatment of this catastrophic illness. If the consequences of the informed consent disclosure about the existence of an alternative therapy is to dissuade people from participating, that is a reasonable societal risk to take in order to preserve the fundamental right of the patient to know the benefits, consequences, and alternatives prior to the patient's being exposed to the experimental product.

In the AIDS drug situation, with a very eager population of persons to willing to experiment with a new drug rather than to face a high risk of fatality, drug sponsors and investigators must be extremely careful in preparing the wording of the informed consent form. Criticism of the inadequacies of an informed consent form, by either the FDA or by the institution or outside critics, may cast an unfavorable light upon the product which is being experimented with in the clinical study. Therefore, drafting of an informed consent in an AIDS clinical trial should be extremely carefully undertaken. Examples of the informed consents which are used by the National Institutes of Health Clinical Center may be appropriate measures of the degree to which a drug sponsor wishes to phrase and to "position" the disclosure about the AIDS drug to the patient.
Section 12.3 - Institutional Review Board Activities

An essential safeguard for the clinical test subject is oversight of the ethical nature of the study. This is assured by the presence at the hospital, clinic or Health Maintenance Organization of an Institutional Review Board (IRB). The IRB is composed of medical scientists, persons familiar with medical ethics, and residents of the community, who cumulatively provide an "outside" review of the ethical status of human drug experimentation done at the institute, clinic, etc. The Institutional Review Board is created under FDA regulation, and must be appropriately formed, chartered, and documented.

When the FDA seeks to verify that a drug has been properly tested in the clinical environment, one of its first steps is to examine the work done by the Institutional Review Board which has jurisdiction for the hospital or clinic. Typically, the hospital or clinic IRB has examined the informed consent, the protocol for this study, the qualifications of the investigator, and other related information, in order to assemble a reliable package of information concerning the drug product.

The IRB does not expressly "veto" clinical studies, but it does strongly recommend to institutional management that management should deny the use of the institution's facilities for the conduct of research which will not meet good ethical norms of patient consent and patient protection. The purpose of the review board is not to act as a barrier, but to advise the management of the institution of ways in which the desired research outcomes
could be achieved without compromising the commitment of the institution to ethical standards of care and responsibility for patient welfare.

The IRB may ask detailed questions about the proposed study, and the investigator and sponsor will be called before the IRB to provide additional details about the benefits which can be expected from the study. In most cases, the IRB does its work carefully, but without disruption of the study schedule, since study sponsors plan the timing of their submissions with an eye toward acceptability to the IRB. For example, the presence of a very solid IRB at a particular institution may induce the sponsors of research at the institution to tighten up their informed consent forms, provide for more detailed medical screening of patients admitted to the clinical study, and otherwise provide adequate safeguards for patients' rights, even before the study is submitted to the IRB for review.

An FDA audit of the IRB occurs approximately once every two to four years. At that time, the policies and procedure of the IRB are reviewed, and particular drug studies are selected for examination. The documentation of the review of each study by the IRB should include a recorded vote of the members of the IRB, or in the event of studies exempted from full IRB review, should include appropriate documentation of the decision made by the chairman of the IRB under the procedures for expedited review which have been established by the institutional board.
In the case of AIDS drugs, when research is conducted at large medical facilities, the "community oversight" component of the IRB might be expanded to include persons from the right risk categories with professional or ethical-norms training. The expansion of the board for that particular study or type of study enhances the willingness of the FDA and of outside groups to accept the credibility of the ethical judgment being made by the IRB. It would be unusual for an IRB to have a basic philosophical disagreement with a clinician concerning the ethical status of the clinician's research. Rather, the IRB interaction with the study investigator is likely to involve a desire for additional patient safeguards, additional consent disclosure, additional record keeping, and the like.

Section 12.4 - Disqualification as a Safeguard

One of the options which the FDA may utilize as a method of enforcing its requirements for the protection of patients' rights is disqualification. Disqualification means that an individual or group can no longer participate in FDA-reviewed research, including new drugs, and new medical devices, new food additives, and the like. Disqualification by the FDA essentially removes the institution, person, or group from any future experimental use of FDA-regulated products. For example, if a hospital has been performing medical research with a drug and it is disqualified on the basis of its IRB's inadequate protection of patient rights, that hospital can no longer perform research with
or any other FDA-approved drug. Inadequacies of the individual investigator may result in that investigator being disqualified from further studies. Or the investigator may, short of disqualification, sign an agreement with the FDA which promises that the investigator will not take on any further research work involving FDA-regulated products, until the FDA has specifically accepted that research to be conducted by that individual investigator.

In case an institutional review board is disqualified, the FDA will no longer permit the institution to perform FDA-regulated product studies. In the case of a university medical center, this could be a most serious setback because of the amount of research typically done through such university centers. The quality of careful review used by the Institutional Review board of a medical center at a university is typically going to be fastidious, because of the concern that if the FDA were to disqualify the institution, a large amount of federal grant and contract money would be lost to the institution permanently.

Disqualification of a sponsor from performing future studies would essentially put a company out of business. A new drug manufacturer, which was disqualified by the FDA from performing any further human clinical experiments, will be stuck with no ability to change its product line, and would probably be sold or enter dissolution because of the sponsor's inability to develop additional products through the FDA approval system. Therefore, the remote prospect of a disqualification of a
sponsoring company for unethical research is considered a "death penalty" in the research-intensive pharmaceutical industry.

Disqualification is rarely used. It may become more frequently used in the course of the FDA's auditing of AIDS-related research. AIDS-related research is of such visibility and high societal importance that the FDA is much more likely to use disqualification as a drastic penalty, deterring other investigators or institutions from permitting inappropriate or insufficiently documented research work at their institutions in the future. The disqualification sanction will typically be avoided by a consent settlement, in which the FDA receives a specific promise by the institution or individual to clean up the past violations, provide detailed reports to the FDA, and in some cases of physician-investigator misconduct, to no longer do any studies subject to FDA regulatory review.

Finally, because disqualification from further medical research can have a fatal effect on the reputation and income of a clinical person or institution, an adequate sense of procedural and administrative safeguards is needed to assure that the disqualification regulations and operations of the FDA are adequately checked by procedural safeguards. The FDA has a difficult job balancing the rights of the individual patient against the due process rights of the institution or sponsor. But it is predictable that in all cases, the FDA will come out on the side of the individual test subject rather than the organizational or professional testing entity. Therefore, disqualification as a
sanction may have more use in the AIDS product cases than it has in other situations in the past.

Section 12.5 - Liability of the Investigator

If fraudulent and false data is submitted to the FDA as the result of the work of an investigator, the investigator may be prosecuted for criminal fraud against the government, under laws which prohibit submitting a false document or false report to a government agency. In the case of AIDS drug, the AIDS drug information is so important to the fast-track NDA approvals, that any false submissions should be considered to have a high risk of contributing to fatal effects among patients. That is, the amount of trust built upon adequate clinical data is so high in the case of AIDS products that an inadequate or insufficient test is likely to trigger FDA investigations, and charges of fraud, and even criminal prosecution.

In addition to the investigator's potential criminal liability for falsifying data which is to be submitted to the FDA directly or through the drug sponsor, the investigator also faces important civil consequences. First the investigator may be disqualified by the FDA, as the preceding section discusses. Secondly, the investigator will probably lose his or her medical license, because it is a serious breach of medical ethics to produce false or misleading clinical data. Third, the drug company will sue the physician for the recovery of the amounts paid for the conducting the clinical studies. This may, for example, be a civil
action for the return of the $70-100,000 paid to the clinical investigator. And fourth, the individual patients may sue the investigator for battery for having exposed them inappropriately to a dangerous drug.

Because of these clinical consequences, and the criminal consequences just discussed, there are ample deterrents that assist the FDA in policing the adequacy of clinical studies for AIDS-related drugs. AIDS drug development carries all of these deterrents, and the stigma of bad publicity as well. When a company, hospital or doctor considers these deterrents, its cooperation with the "system" is more likely. Temptations to "buck the system" exist in these arenas, is as in all medical research fields. Fighting these temptations is far more likely when the would-be maverick weighs the FDA's potential "adverse reaction" to such free-style research.

Section 12.6 - Patients' "Right to Know"

The patient has a right to review his or her medical records from the clinical trial after its completion. FDA respects this right, and most sponsors will readily agree to share the records with the personal physician of the former study participant. But during the study, a patient might be influenced too much if he or she were given the code-breaking information of which substance was actually being dosed. As FDA said in an October 1988 press statement, the use of codes in studies helps "avoid errors in determining results caused by over enthusiasm or
other forms of bias among patients and investigators." So the patient gets a copy of the informed consent document but does not know until after the study whether his or her dose was actually the chemical entity being tested.
The approval of a new drug generally requires a succession of human clinical studies intended to generate detailed information in controlled, documented studies. This has been the pathway of drug development since 1962. The emergence of rapidly-evolving diseases such as AIDS, and the desperate need for experimental drugs to assist with the treatment of AIDS-related patients, led the FDA to create the "Treatment IND" in 1987.

The difference between a Treatment IND and a regular IND is that the Treatment IND does not involve a particular approval process for the product, such as would be the case with a university or clinic in which a research study is being done in order to win approval of the product. The treatment IND is expressly intended for diseases which are immediately life-threatening. It is not literally an IND, but is a protocol for nontraditional administration of an investigational drug. The treatment protocol is often just part of a larger, conventional IND program.

The FDA, in its May 1987 final regulations, cited "advanced cases of AIDS" as examples of the types of experimental drugs for which Treatment INDS would be appropriate. FDA noted
that an anti-retroviral drug might be found to be appropriate, on the basis of Phase II human safety studies, for the control of future progression of patients from the asymptomatic state of HIV infection into future states of clinical signs of the AIDS disease. If the drug were capable of retarding the progression of disease, then a Treatment IND would be appropriate, because the drug would meet FDA's definition of an illness in which premature death is likely without early treatment.

There are two kinds of Treatment INDs: those sponsored by a manufacturer which is a traditional drug-developing company, and those which a licensed physician sponsors. The individual doctor's request for a Treatment IND asks the FDA to grant him or her permission to conduct a small-scale study, incidental to patient treatment, as the sponsor-investigator. FDA will look closely at that person's qualifications before granting permission.

Controversy over the treatment IND process will continue as long as there are patients who want experimental therapies but who are not within reach of the controlled clinical trials site. FDA expressed the view in an October 1988 press statement that "the fastest way to develop a drug is with carefully controlled clinical trials . . . The more open-end the design of a clinical trial, the less likely the chance the trial will provide answers." So the movement toward treatment INDs is a humane accommodation of needs, not an encouragement of the shift of research efforts into the open-ended operation of larger and larger studies.
Section 13.2 - Criteria for Granting a Treatment IND

The FDA will allow the use of an IND drug for AIDS or other serious and potentially fatal diseases if FDA determines that (1) there is an appropriate use for the drug under an IND; (2) active research for marketing approval is underway "with due diligence", and (3) "there is no comparable or satisfactory alternative drug or other therapy available to treat the state of disease in the intended patient population".

Under these restrictions, it will be rather unusual for a Treatment IND to be sought by a drug company. Instead, physicians treating persons who have the illness will seek out the drug company and ask the drug company to file a Treatment IND for their benefit. As a matter of economics, it is not in the long term interest of the pharmaceutical manufacturer to seek Treatment INDs. Rather, it is a matter of human values and sympathy for the pharmaceutical company to permit treatment use of its investigational new drug.

The IND drug could be made available if indeed there is no alternative for this serious and fatal condition. The manufacturer who has such a product which is believed to be appropriate should be willing to permit its use for the appropriate treatment under IND controls. However, the manufacturer still will have to maintain and provide the FDA the appropriate treatment reports. Therefore, the treatment IND increases the likelihood of adverse effect reporting and may delay the final approval of the
The sponsor of the Treatment IND must submit to FDA a mini-set of the same types of documentation that will be filed for the IND or NDA. The amount of information is considerable, and the same standards of quality of care, informed consent, and institutional review board oversight will apply. This volume of information poses the same hurdles to be overcome by the drug sponsor. It is not likely that the drug sponsor will enter into a treatment protocol submission and product approval without a careful examination of the pro and con factors involved in such a drug study.

The treatment protocols submitted by the Treatment IND sponsor are subject to the same review by FDA, with the same process of examination, potential "clinical hold" and FDA auditing of date, as would be the case for a larger IND experiment. The Treatment IND, by comparison, involves much the same paper work for the benefit of a much smaller group of patients.

Normally, clinical trials of an investigational drug do not involve patient payment for the drug product. The patient receives the product free from the clinical investigator.
In the case of Treatment INDs, and especially of the high-cost fabricated drug products which have been used for AIDS-related uses, the FDA will permit authorization for a charge for the investigational drug if the sponsor has requested specific permission to do so. A review of the FDA provisions on economic cost recovery for investigational drugs [Section 312.7(d)] will show that FDA has a procedure in place for approval of charges, but one can readily infer that the FDA does not wish this process to be utilized. The sponsor or investigator may charge for the drug under a Treatment IND if the FDA finds that this is not "commercial marketing" and the sponsor is diligently pursuing active marketing approval. FDA has the opportunity to challenge the adequacy of that expense, and to make certain that the charge for the drug is adequately considered.

It would be politically unacceptable for the FDA to permit charging for the AIDS investigational drugs, unless the FDA were to get deeply involved in the financial status of the product and the manufacturer. The FDA in its May 1987 statement relating to charges for Treatment IND drugs said that FDA "should not be put in a position of being a price regulator" and therefore FDA will stay out of the actual pricing so long as it is not "larger than necessary to recover the costs associated with the manufacturer, research, development and handling of the investigational drug".

FDA is, however, very aware that the sponsor may be tempted to leave the product in the investigational phase as a means of getting a steady stream of income without the cost of
product approval. For that reason, FDA requires the manufacturer to use due diligence to pursue approval of the drug product. The sponsor can obtain FDA's permission for the charge, but because of the detailed safeguards for such drugs against commercial marketing, advertising, and product activity, FDA will expect to monitor this practice. Ultimately the dollars earned by charging may be less than the value of the regulatory hassles incurred to set up the FDA-approved charge mechanism within the IND.
CHAPTER 14

The New Drug Application

Section 14.1 The New Drug Approval Process for the AIDS Drug

The stages of clinical, animal and bench chemistry research discussed in the preceding chapters ultimately lead to the main event - filing of a new drug application ("NDA").

Many persons infected with the HIV virus are concerned that the process of new AIDS-related drug approval is too slow. The NDA process of the Food and Drug Administration is a painstaking process, set up in its basic form by Congress (and closely reviewed by Congress on many occasions) in order to make certain that drugs which are approved for human use in this country are as thoroughly tested and examined as possible before they reach human recipients. The emphasis in countless oversight hearings has been upon conservative FDA review, challenging some product approvals for having been too quickly granted. Indeed, Congress never applauds fast, efficient approvals. The focus of this Congressional criticism has been on excessive risks being taken in the granting of an NDA. Each phase of FDA review has been challenged as insufficiently cautious, in separate Congressional hearings. It is no surprise, then, that FDA is so conservative when deciding on product approvals.
This Congressional oversight has encouraged caution, delay, and detailed data review. It is relatively rare that Congress sets up a particular set of criteria in the text of a statute. Usually, the method of implementing a social goal such as the assurance of drug safety is done by a broad delegation to an administrative agency. In the control of new drugs, however, the Congress has been explicit in requiring the manufacturer to file a new drug application for the specific type of drug, the specific dosage, specific label, etc. Then the FDA reviews the specific requests for approval and makes an approval decision which is very particular and very specific. Because the new drug application processing is so specific, and because science has evolved to a state of new and rapidly changing discoveries in medicine today, the approval of an NDA is a much more difficult task than it was when the first NDA were filed after the passage of the 1938 Food, Drug and Cosmetic Act. The NDA today is a massive, multi-file cabinet sized submission, the size of which often dwarfs the individual reviewer assigned to that particular NDA.

In light of the finality of outcome with the AIDS disease, the approval process for AIDS-related drugs has been expedited (as we discuss in the following section), but Congress has not relaxed the NDA review process set up by legislation. Even though FDA can expedite the clearance process by giving favored treatment to NDA drugs for AIDS, processing each NDA is an extremely difficult bureaucratic task. The private sector role in
the review tests the endurance, patience and responsiveness of even the finest pharmaceutical houses. It is no wonder, therefore, that the burden of filing an approvable NDA is often seen as an insurmountable barrier by smaller research-oriented manufacturers who wish to bring an AIDS product into the marketplace.

The NDA process for AIDS-related drugs is, at least in structure, no different than approval of a drug for arthritis, the common cold or cancer. What will be different is that the attention paid by FDA to expediting product clearance is remarkable in the case of AIDS drugs. Drug development has many open questions. Delay of an NDA is often the result of FDA's desire to answer all open questions before approval. For AIDS-related drugs, FDA simply decides to defer all but the most important questions until after the drug's approval. The questions are still the same; postponing their answering is the difference in the AIDS-related drug approval process.

FDA's intensity of involvement in terms of personnel, structure, monitoring and senior management oversight is exceptionally high in the AIDS-related drug approval process. The frustration which comes from the very lengthy drug development process is a reflection of the 1962 Congressional judgment that "all drugs are created equal," and only those drugs that have thoroughly established their effectiveness can be licensed for widespread human use.

Until and unless Congress changes the law to recognize distinct approval criteria which are easier to review for specific
drug categories or specific diseases such as HIV infection, the strong likelihood is that NDA approval will remain a difficult hurdle for the AIDS-related drug category.

Section 14.2 When is the NDA Filed?

A misconception may exist that FDA's delay in handling an NDA is a result of premature filing, before the company sponsor has enough data. In fact, great volumes of data must exist before the NDA can even be drafted. The NDA is typically filed after the conclusion of animal tests, human safety studies and two adequate and well controlled clinical studies. All of their attendant and precedent documentation will need to be completed. The sponsor completes the chemistry search, the animal studies, the studies in healthy volunteers, the studies of safety in patients, and the studies of effectiveness in patients, before filing the new drug application.

Timing of the filing of an NDA for new drug varies with the type of drug and the number of "loose ends," the unanswered questions which remain after the manufacturer has completed its Phase III effectiveness studies. If the manufacturer has left questions unresolved, there may be a delay, in the form of voluntary withdrawal of the NDA, until adequate answers have been found for the missing questions. On the other hand, when expediting a particular drug is essential for its much-needed therapeutic benefit, the drug's special review process may include speeding its NDA along, even before the total paper work is
completed for the Phase III effectiveness studies. The decision to move faster with the NDA includes a significant risk that a prematurely-filed submission, which does not answer the anticipatable questions of the FDA, will be rejected as incomplete, and will be sent back for further work by the responsible firm. Therefore, the choice to move ahead to expedite the new drug application itself carries with it some significant downside risks for the drug developer. The AIDS-related drug has two advantages: an option to skip Phase III while developing efficacy data in Phase II, and FDA's willingness not to require that all answers be in hand to all questions before approval.

The timing of NDA filing is not always controlled by the scientists involved. Rather, in some cases, the investment aspects of new drug development become more important for the particular manufacturer. Investment houses studying share value of small, medium or new drug development companies want to see rapid progress toward new product approval. Approval to market brings income, income brings higher shareholder value, and higher shareholder value brings success to the company.

The hasty decision to speed ahead with an early request for product approval can cost a considerable amount of time and embarrassment, however, if financial concerns have pushed for approval faster than science can demonstrate support for such approval. If a new drug application is filed before the company has completed its analysis of the data, or if the company recognizes that missing data needs to be developed, but proceeds
to the NDA stage anyway, then the company has wasted its time and
that of the FDA on an incomplete project. This incompleteness of
the NDA filing has not yet been significant for the AIDS-related
drugs, but it would become a serious problem if AIDS-related drugs
were pushed into FDA review for the purpose of artificially
boosting financial or shareholder objectives, rather than on the
schedule for submission that would be merited by the particular
status of the particular drug.

Two external factors influence the timing of a sponsoring
company's filing of a new drug application. The manufacturer
seeking sales opportunities is concerned to get to the market
before its competitors can develop a similar drug. The appearance
on the near horizon of a competitor's new drug application may
stimulate speed on the part of a new drug company sponsor.
Secondly, the insistence by the National Institutes of Health, the
Food and Drug Administration, and the Centers for Disease Control
upon a rapid development of an AIDS treatment is an element which
must be considered. The point is well taken in the context of an
AIDS drug when the sponsor is encouraged by the FDA to take the
product directly from clinical trials into the NDA approval
process, so as to expedite the FDA's approval of that beneficial
chemical entity.

The typical delay between NDA filing and NDA approval is
approximately two years. For the successful AIDS-related drugs,
FDA hopes to reduce this NDA filing/approval timeframe by one-half
or even two-thirds. But NDA approval is not a rapid process,
scientifically or legally. A cautious approach by the FDA is to be expected.

Section 14.3 AIDS Drugs and the Approval "Fast Track"

FDA managers decided at the end of the 1970s that they needed a mechanism to better track the flood of new drug applications, so that FDA would prioritize which of the various applications merited expedited treatment. Drugs were classified according to their status as "new chemical entities," or those imitative products which were not truly "new." The least innovative products received a rating of 5, and the most innovative a rating of 1. Another scale measured the importance of the drug, with a "breakthrough" drug (e.g., one which changed the therapeutical or pharmaceutical picture for a particular disease) being rated "A," while a simple "Me-too" drug received a letter "E" classification.

Until AIDS drugs came along, the most important breakthrough products for heart disease and cancer received 1-A status. Recently, FDA created the special 1-AA category and has treated these special drugs on the "fast track" in terms of prioritization. Category 1-AA drugs receive rapid movement from the chemists, medical officers, and toxicologists within FDA, and these proposed drugs' NDAs receive very rapid review of their findings and expedited approval by FDA managers.

From the point of view of persons with the HIV infection, the fastest possible timing may not be soon enough. FDA's fast
track is still slower than that of other countries, which check for safety but are not as insistent upon statistically significant proof of product effectiveness. The FDA, according to its mandate from Congress, must obtain and review a set of valid data concerning product effectiveness before the AIDS-related product is ruled an "approvable" new drug. This legislative command to develop that effectiveness data is the principal reason why FDA does not speed up the process to an even greater extent. Within that limitation, when an AIDS-related drug is brought before the reviewers for action, it moves to the top of the reviewing FDA official's agenda.

The reader is cautioned that any decision that AIDS-related drugs should be on a "fast track" does NOT mean that the products are less safe or less effective than those products which have languished in the FDA system for several years. The very intensity of the scrutiny that is given to a product which claims to have effectiveness against a dreaded epidemic is likely to pose such a visible management challenge that FDA managers will pay close attention to the findings of the study about that particular drug. What does occur differently is timing; efficacy questions are postponed for later post-approval studies, and do no hold back approval. The AIDS-related drug documents move rapidly through the paper-processing system in the FDA while other non-AIDS-related NDA's are put on hold.

The best example of the "fast track" for AIDS-related products was the approval of AZT, the drug zidovudine. That drug
was reviewed by the FDA and approved in very rapid time, with the pre-clinical tests beginning in 1984, the IND submitted in 1985, the Phase II studies begun in February 1986, and a total exception or waiver from Phase III studies. The new drug application was submitted in December 1986 and the drug was approved in March of 1987. In this rare case, the entire effectiveness time span was saved because it appeared that patients in the earlier phase II trials were clearly living longer than those patients who were given a placebo. It was deemed unethical to continue to withhold treatment from the control group, according to the FDA, and therefore the product went on to the NDA process without going through the double-blind clinical research studies or its effectiveness. If survival is the end result of the AIDS-related drug study, it serves no purpose to delay the research once increased survival rates are shown.

Of course, for every product which receives such extremely rapid approval, there are dozens which are delayed for years. There is even some resentment of the priority for AIDS-related drugs among makers of products for ulcers, arthritis or other illnesses, who find that the time and attention paid to their products is significantly lessened because FDA reviewers and supervisory officials are devoting much more attention to the urgent need for the AIDS drugs.

An additional advantage of the level of close scrutiny given to AIDS-related drugs is that unresolved questions will come early and often. Many of the delays discovered in the course of
dealing with a normal or traditional drug product were avoided in this class. Weak points were rapidly isolated, and immediately discussed, as a result of close interaction between the FDA reviewer and the pharmaceutical sponsor company. The pharmaceutical company has an incentive to make sure that the questions from the FDA are listened to, clarified, and responded to. These interactions between the drug sponsor and the FDA take on a very high priority when the AIDS drugs are at issue. FDA itself will expedite the NDA review process, and it expects that the manufacturer of the drugs will hasten its own tasks of preparing the NDA documents. The better the documents, usually, the more rapid the approval will be, once the product reaches the top of the "in box" for the FDA reviewer. FDA's rapid review can only occur if data about the proposed product is soundly prepared by competent sponsor personnel.

Section 14.4 How the NDA is Structured.

The new drug application is a compilation of many separate documents, with one unifying theme written in its opening summary. The art of drafting a summary for an NDA submission involves the ability to clarify the confusing interplay of many different sections of the compilation, so that the reviewer can quickly get to the heart of the product benefit claims asserted by the product's sponsor. The summary is a detailed explanation of the documents to follow, and the manufacturer in writing the summary should use all the available methods of clarifying,
FDA requires the NDA's summary to include the proposed labeling for the drug, including the manufacturer's expectations of the kinds of claims which would be made for it. The summary will include statements concerning the intended use and clinical benefits of the drug, descriptions of the history of the drug, and then the details. These details include chemistry, manufacturing, quality control, animal study findings, human study findings, microbiology (in the case of an antiviral product), clinical data summaries, and this necessary conclusion: "A concluding discussion that presents the benefit and risk consideration related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct post marketing."

From the viewpoint of the sponsor, time spent in preparing an adequate summary and an adequate description of the NDA will be well spent. FDA will break apart the pieces of each NDA compilation and give portions of that compilation to chemists, to medical reviewers, to pharmacologists, to manufacturing experts, to field inspectors for on-site investigation, and to other specialists who will be brought in to examine their respective segments of the NDA compilation. It is very important that the sponsor of the NDA present data understandably, so that each of the different reviewing disciplines is able to discern readily in the document what the key findings of the research had been and what the key claims or presentations are on the part of the drug.
sponsor. The blend of clarity, accuracy and persuasiveness is a difficult challenge for technical writers.

In the case of an AIDS drug, for example, where the antiviral effects are centrally important, the key segment on microbiology must be carefully written and carefully summarized. The data relating to the microbiological activity of the proposed drug must be written with particular care, because it will be examined thoroughly by the FDA microbiologists who are responsible for that category of anti-infective drugs. The NDA segment on quality control steps to be used will be extremely important if the product is one which is easily contaminated, or easily becomes ineffective if not completely purified or processed during the manufacturing phases.

The mistakes in any particular NDA which cause delays will vary from situation to situation, but most frequently, it is the reviewing medical officer of FDA who finds that inadequacies exist in the proffered data concerning the clinical trials. A clinical efficacy trial for a drug is not only the NDA application's most expensive and time consuming portion, but is also the most persuasive support for approval. Summaries of the clinical trials, graphs and visual portrayals of the findings and other methods of clear presentation are extremely important in avoiding unnecessary confusion concerning the AIDS-related drugs.

The label claims which the manufacturer lists in the initial filing of the new drug application may be significantly broader than those which are finally approved by the FDA at the end
of the process. The FDA is much more likely to constrain the permissible indications for use, and lower the promotional expectations of the drug, as a cautious, conservative agency should do. The manufacturer often makes a choice at the beginning of the process whether to claim effectiveness in "borderline" situations on the labeling, and in some cases sponsors do not make claim in order to get by the initial efficacy proof barriers easily, hoping that they may come back to supplement the new drug application at some subsequent time for the particular disease condition which is of greatest interest to the drug developer.

In the case of the AIDS drugs, fulfillment of label-promised benefits is critical. FDA will pay close attention to the kinds of labeling claims that are being made for the drug. If the drug is intended to work with symptoms exhibited by persons already infected with the HIV virus, then the manufacturer's phrasing and context of the claims will be closely examined by the FDA's advertising reviewers. FDA will not clear an NDA drug whose label would "over-promise" relief to the anxious HIV-infected purchaser/user.

Section 14.5 The Review Process

For AIDS drugs, the review process is much more efficient, stimulating, and expedited than for other drug products. Typically, an NDA filing is distributed among a team of reviewers after it is broken out by type of document, e.g., the chemistry section will go to a FDA chemist, the labeling section to a FDA
advertising review specialist, and the like. The AIDS team approach has been very effective in expediting the IND and NDA stages of drug approval for AIDS related drugs.

FDA's approach to review of AIDS drugs is much more simplified. A team approach, with meetings and hierarchical reports flowing to the upper management of the Drugs Center in FDA, is a means of expediting product approval. The FDA chemists, medical officers, and other reviewing officials will meet frequently to determine what additional documentation is necessary. The team's coordinating person (usually a Consumer Safety Officer) takes the questions of the physicians and toxicologists and communicates them to the corresponding officials at the product sponsoring company. FDA uses this expedited means of team review so that there is no basis for a later allegation that the FDA had "dragged its feet" on AIDS cure, by referring the total package in slow sequence to one part of the FDA after another. AIDS drugs do not receive such a sequential review, but instead receive the expedited team-supported review.

There is no "typical" AIDS drug product. But participants in a typical reviewing division can be identified. The paper work will be the responsibility of the teams' Consumer Safety Officer. The medical questions and especially the patient efficacy determinations will be the subject of medical officer review, with support from a bio-statistics organization. If there are serious doubts about the accuracy of the conclusions drawn, these are fed back by the physician Medical Officer to the Consumer
Safety Officer, and then are reviewed with the company in a meeting, or passed along to the company by telephone or by letter. For AIDS drugs, the usual transmission delays in the system are reduced. FDA stays in virtually constant contact with the AIDS-related drug sponsor. Documents and letters move rapidly, and are not lost in the shuffle as may occur from time to time with other drug products. Using management analysis and tracking systems, FDA has recognized many of its procedural bottlenecks in the drug approval process and has dealt with them competently, so that the AIDS drugs are not held up by unreasonable delay or unnecessary levels of review. The FDA Commissioner personally tracks AIDS-related drug NDA's on his personal computer, and emphasizes the priority of AIDS-related drug issues frequently.

The Medical Officer has the primary role in the review of the proposed drug product. This physician is responsible for evaluating the human clinical response, and for identifying additional factual issues which remain to be established. The pharmacologists, chemists and others can comment adequately on the manufacturers' proposed plans for establishing a continuing manufacturing process, and the field investigator can determine whether the plant which is currently operated by that drug manufacturer could reasonably be expected to produce that specific drug at a consistently high quality rate or with a low level of deficiencies during full-scale manufacturing. The team of FDA officials works together on the AIDS-related drug to expedite the movement of documents and handle most of the questions and answers.
If an FDA Medical Officer leaves a team, the NDA may not move ahead until new personnel or workload adjustments occur. Teams on AIDS-related drugs are expected to have more staff and lower personnel turnover. However, drug developers' higher salary offers may be increasing FDA's rates of personnel turnover for these highly skilled and experienced physicians.

Dialogue between drug sponsor and reviewers occurs at formal meetings, as well as by dozens of informal (often telephone) contacts. Meetings to discuss the AIDS drug are much more frequent than meetings for a normal illness-related product. FDA wishes to expedite the process, and will waive test requirements (such as the Phase III studies waived in the case of the drug AZT) in order to get an expedited approval. The "heat is on" both industry and government participants, so normally cool relations are warmed and expedited.

FDA frequently will take the new drug application, after its review by the Medical Officer, to an advisory committee. The advisory committee, composed of outside experts who are paid a nominal sum to participate in the process of FDA drug review, make important contributions to the FDA's factual determinations concerning the drug. If the FDA staff has a question concerning the probable clinical outcome of an excessive dose of the drug, for example, there will typically be members of the advisory committee who can advise the FDA about that potential risk, on the basis of their clinical practice experience.
Following the review by the FDA operating division, and perhaps advisory committee examination of the new drug, the process of official approval begins. Once the drug is recommended for approval by the review team, the Division Director of the FDA drug reviewing division then writes his or her recommendation concerning the product, which goes up through the Office Director to the Center Director. At each stage of product approval, the manufacturer of the AIDS drug can expect to field additional questions. These additional questions are likely to be relatively easy to answer, but in this case, the officials who ask the questions fully recognize that rapid acceptance carries some risk. The FDA officials will be criticized if an AIDS drug is expedited onto the market, and then causes a very severe set of adverse reactions which had not been detected or predicted by the rapid clearance.

The final approval power over a new drug has been delegated to the FDA Center Director, although under the law, approval begins as a power of the Secretary. The Secretary's power flows down to the FDA Commissioner, from the Commissioner to the drug reviewing organization, and then the signature needed for product approval is that of the Office Director.

An additional distinction in the timing of the AIDS drug is that the Commissioner and other officials of the Department of Health and Human Services have political and public relations benefits for expedited approval. Managers within the drug reviewing divisions should feel that sense of political and
societal demand for an AIDS treatment, as one of the factors in their review. To the extent that such pressure from higher authority has a beneficial impact, the sponsor of the drug is benefited.

Section 14.6 - Additional Study Requirements

Because the congressional mandate to the FDA is for approval of products which have proven their effectiveness and their safety, FDA can expect to reject many applicants for lack of proof. There will be a considerable number of drugs which go through the IND process but which fail to prove their efficacy. When the NDA is filed, it is not accepted. This application then recycles, often more than once, as the sponsor seeks to respond to FDA's concerns that its data is not complete. The complete answer to the FDA's question may be needed before the product can be approved.

The sponsor rarely fights the FDA over the concept of a need for comprehensive safety or adequate effectiveness evidence. These basic needs are well understood by all sides. It is the application of these needs to the specific application at hand which causes the frequent disagreements between sponsors and the FDA. The sponsor believes that its showing of effectiveness is adequate. The FDA medical officer does not believe that the statistical showing of effectiveness is sound. FDA biostatistians and those of the company may come up with very different conclusions, if the patient population did not show an extremely
clear and convincing improvement as a result of the exposure to this product.

The demand for additional studies is usually presented to the sponsor in the form of a request that the company should withdraw the NDA and resubmit with additional studies. The format of this request is legally significant. A withdrawal of the NDA is a "voluntary" act by the sponsor. The statute allows FDA 180 days within which to take an action after filing of the NDA. FDA seeks to treat the filings as incomplete, whenever possible, so as to allow the reviewer additional time. In the AIDS cases, however, this is not really an option. The FDA is directed by its management to expedite the approval of AIDS drugs. Additional studies may be done subsequent to product approval, under an agreement between the FDA and the sponsor which calls for additional studies in what might be called "Phase IV". Or the studies that are in place may be inadequately explained in the biostatistical section of the NDA. The FDA drug reviewer may then recommend that the FDA not accept the summation of the data presented by the company, unless and until that summation is reviewed and revised to meet expectations of the FDA medical officer.

What will it take to win approval? An actual additional study, or merely the statistical reexamination of data from the past studies, may be what the FDA wants at the time it calls for additional research work on the part of the drug sponsor. Without that additional work, it is very likely that the FDA will not grant
the requested approval for an approved new drug application. The cost of doing the additional studies, and the time delay inherent in withdrawing one's new drug application, might be avoided in the AIDS situation if the drugs are under NIH grants. It may be that the NIH category of drugs benefits significantly compared to normal commercial research, because in some cases the FDA gives the National Institutes of Health the "benefit of the doubt" for its work with AIDS patients. The detail of additional studies needed may not be as frequently cited in refusal of NIH INDs as they would be for private submissions. This is because the NIH has sufficient incentives to be careful in conducting the studies, regardless of the time or cost involved, but the same cannot be said of all manufacturers.

Section 14.7 - Role of the Advisory Committee

The advisory committees to FDA's Center for Drug Evaluation and Research are very important sounding boards. FDA uses the members of its advisory committees, depending on the category of expertise involved, much more frequently than at meetings alone. FDA could consult with members of the advisory committee, could send portions of the documents to be reviewed to the advisory committee, and can also in some cases use the recommendations of the advisory committee as a "foil" to offset pressures from the drug reviewer, the drug industry, or other persons concerned with the AIDS drugs.
The members of the FDA Advisory Committee are selected for their impartiality, lack of connection to sponsors of drugs pending before the FDA, and expertise. Expertise is not necessarily the first criterion for advisory committee membership, since FDA may give to the same of expert advisers a variety of drugs in a variety of set classes of therapies. The advisory committee typically meets three to five times per year, addressing new product reviews for those particular questions on which FDA wishes its advice. Presentations can be made to the panel by industry or interested persons (where confidentiality rules would permit, in public session) and the advisory committee could recommend that the FDA speed up its approval of a particularly valuable product because of the need for that product in clinical settings from which the advisors are drawn. The advisors are a channel into FDA's reviewers by which the reality of clinical practice is introduced into the often-esoteric efficacy decisions of FDA review.

Section 14.8 - Labelling and Claims

"Labelling" includes package or carton labels, the "package insert" brochure, any brochures for patients, or any other descriptive documents which accompany the drug to the prescriber. The new drug application's labelling section states in draft form what the physician who is considering that drug would see when making the decision to prescribe it. The physician will look to the label, to brochures, to the Physician's Desk Reference, and
other descriptive documentation, to understand potential adverse consequences, contraindications, and rules for safe dosing. This set of information will be found in the labelling and claims proposed by the sponsor discussions in the NDA filing.

The initial NDA claims are not necessarily those which will ultimately appear in the market. That is because the FDA's drug advertising group reviews each new drug's proposed labelling cautiously, and will limit or subtract from those claims if FDA feels consumer or physician deception might occur. A particularly broad indication cited for the drug, such as by making a mouthwash claim for "Kills the AIDS Virus" out of ordinary mouthwash, would draw close scrutiny. The labelling claims should contain sufficient exclusions and limitations so that the claims will express actual, identifiable benefit to the consumer, as well as some limitation on the use of the product where the FDA or its advisory committee feels the use may be contraindicated.

In many cases, the product's deficiencies noted in the medical reviewer's examination of the clinical trial data will be added into the labelling. Because the human clinical trials showed some gaps or weakness in product effectiveness, the manufacturer is required to put into the labelling a limitation on the use of the drug which suggests that the prescriber not use it for a particular application or for a particular set of patients. Use of the labelling as a means of limiting use of the drug is a well established practice to control potential problems with prescription pharmaceuticals. The physician is free to prescribe
the drug for a use which is not in the labelling, if he or she chooses. In the case of an AIDS drug, warnings against a certain use are very likely to be utilized as a means of avoiding those situations in which the product will probably not deliver the benefit that the patient might expect.

A final benefit of the claims and labelling portion of the NDA is that it reduces unreasonable expectation before they begin. The manufacturer is likely to start with very strong claims, but the FDA limits those claims to only those which are factual substantiated. As a result the manufacturer's final claims are very close to the provable objective truth.

Section 14.9 - Final Approval Steps

The review of the drug through formal channels at FDA headquarters, including a side excursion for an advisory committee review, is not the only interaction between the FDA and the company. Before the product may be approved, FDA must be certain that the manufacturing site is adequate to consistently produce high-quality doses of the drug. Therefore, as part of its checklist for approval of the drug, the FDA examines the manufacturing site and makes a determination that the manufacturer is capable of the adequate quality control needed to produce its drug in an appropriate manner, over mass production quantities, with uniform quality.

The inspection reports on manufacturing controls become part of the approval package. The individual reviews of the
chemist, medical officer, statistician, and other reviewing officials are brought together in a review document which goes to the Division Director. From the Division Director it is reviewed by the Office Director (such as the Office of Drug Evaluation) and ultimately is brought to the Director of the Center for Drug Evaluation and Research.

At each stage of approval of the AIDS drug, the pressure is likely to increase. The individual medical officer and the review team can make a relatively objective judgment about whether sufficient factual data exists for approval or disapproval of the effectiveness of this drug product for these claims. Beyond the level of this objective data, when particular negative factors must be weighed against the societal need for an effective AIDS drug, managers at the level of Office Director and Center Director get heavily involved. The weighing and balancing power which is delegated by Congress to the responsibility of the Secretary of Health and Human Services is actually borne by the Center for Drugs Director and his or her staff.

Once a decision has been made that the drug merits approval, a letter is issued informing the sponsoring firm that its product is approvable, and that the sponsor should make last-minute changes in the drug labels. These last minute changes can be extremely important in future sales or promotion. But the company has an overwhelming incentive to get the product to market, and FDA advertising review officials may take advantage of that incentive by requiring the scope of the claims or indications to be limited,
or FDA may ask for other variations in the product label. These changes are virtually always accepted by the manufacturer in the interest of speed for moving the product onto the market.

The final approval stage for the NDA is the issuance of a letter of approval, signed by the Center Director or in the case of the more controversial drug, perhaps by the FDA Commissioner himself. The product approval then is final, and the product can be sold. FDA will publish the approval letter in a listing issued on a monthly basis. These approvals of drugs by the FDA are a matter of public record, and interested members of the public can read from the list which products have been approved. Competitors can go beyond the list to request copies of summaries of the safety and effectiveness data upon which the product letter was premised. Before the approval letter is issued, however, FDA procedures for confidentiality do not allow the general public, or competitors, to see the supporting documentation or the FDA reviewer's conclusion concerning the reviewer's portion of the drug review.

For the AIDS-related drug, the delays and uncertainties involved in typical NDA approval are significantly lessened in the final approval stages by the classification 1-AA. That special status of the pending application moves the Division Director, the Office Director and ultimately the Center Director to expedite the blessing of the agency upon the new drug product. Having that advantage, the drug is much more likely to move through from medical officer review to approval for marketing, without the
significant delays often found in higher management review stages
of pending new drugs.

Section 14.10 - Withdrawal, Rejection and Protest

As with any governmental process, some proportions of
the new drug applications filed are not accepted by the government
agency to which they are addressed. The Food and Drug
Administration regularly rejects new drug applications, using the
informal grounds that the manufacturers "has withdrawn them" for
the development of additional information. In practice, the FDA
has an exceptionally good bargaining chip. The courts defer to the
wisdom of the FDA, and do not judicially review the decisions by
the FDA that a particular product needs more substantiation of its
factual claims of effectiveness with close scrutiny. Therefore,
the FDA is going to win a dispute about a drug, and the
manufacturer has relatively little leverage to challenge the FDA
decision in the courts. When an NDA is considered incomplete by
the FDA, and is being sent back for additional work, manufacturers
will typically accede to the request, withdraw the NDA, and
resubmit it after the additional questions are answered or the
additional studies are performed.

In rare cases, a new drug application which the FDA
considers to be incomplete can be "filed over protest", in a
situation in which the manufacturer and the FDA cannot agree
concerning whether the problem has been appropriately documented
in the NDA. Before a new drug application is filed over protest,
the manufacturer usually has successively sought to have higher levels of FDA management involved in meetings at which the company and the FDA staff can demonstrate their disagreements about the product's readiness for NDA review.

If an NDA is filed over protest, the FDA will formally examine the adequacy of the product and will make a determination about whether the NDA is approvable. However, as a matter of reality, any product which is filed over protest has virtually no chance of becoming approved by the FDA. The procedure is in place so that in an appropriate circumstance, a manufacturer who wished to do so could establish a legal basis upon which to seek judicial review of the denial of the NDA. It appears to be a futile gesture.

In the most rare cases, in which the manufacturer does not withdraw the NDA, the FDA may merely reject the NDA outright. There are grounds expressed in the statute for rejection of NDAs, the most likely of which is that the manufacturer has failed to prove that the product will be effective for its claimed indications. In the case of an AIDS-related drug, this recital will typically be the situation where the manufacturer claims effectiveness against pneumonia, degenerative nerve problems or other symptoms of clinical AIDS. If the FDA rejects the NDA, the NDA sponsor may challenge the FDA decision in court. This will probably be futile, however, the decision is a matter of procedural due process, and sponsors have on occasion challenged the FDA in the courts.
In the case of AIDS-related drugs which are developed by smaller, more innovative manufacturers, it is probably unthinkable that a manufacturer could win any challenge to an FDA rejection of a new drug application. It is much more likely that the manufacturer will seek to accommodate the FDA's wishes, withdraw and resubmit the new drug application, and continue a cooperative effort towards the development of a drug for the HIV virus or for the particular symptom at issue. In most situations, FDA would not reconsider a full outright rejection of a new drug application. It is both tactically and legally prudent for the drug manufacturer who is interested in the long term development of an AIDS product to cooperate with the FDA rather than to fight over the FDA's insistence on the additional studies. The cooperation can pay dividends when the FDA later is faced with a "judgment call" about the company's application or another application for another drug. Cooperative attitudes by manufacturers are an intangible but important factor in future drug approval decisions.

Section 14.11 - Improvements to the NDA System

Criticism of the NDA system have been one of the few truly consistent factors in drug law over the last 50 years. There have been criticisms of the requirement for pre-approval of all new drugs since the requirement was first added by Congress in 1938. The arrival of AIDS on the scene, intensified by the lack of any "magic bullet" solution to the illness, has increased the criticism of the new drug application process.
FDA, and especially its career managers, are politically quite savvy about criticism of their processes. The FDA's approach to criticism is to restate the internal changes which have been made to expedite the highest-priority drugs such as those destined for treatment of AIDS-related conditions. FDA can point to significant reductions in its backlog of pending NDA's. FDA Commissioner Frank Young has pointed with pride to the accomplishment of many of the action plan objectives which he put into place in 1986.

With specific regard to AIDS-related drugs, simplification of the document flow would be a major accomplishment. FDA is moving toward computer-assisted data flow programs, under which the reviewer could examine and correlate pieces of data in a way which would answer efficacy questions with minimal searching through the volumes of clinical patient reports for bacteriological or chemical documents. FDA's approach to this paper-handling process had been widely acclaimed among insiders familiar with the FDA practices of past years. However, paper handling is not the same as people handling. The FDA definitely needs an additional complement of trained physicians and pharmacologists to make the workload of drug review more tolerable, and to increase the attention that is given to high-priority drugs. If sufficient scientific personnel were available (in 1987, FDA lost 15 medical officers and gained 30) then incremental improvements in time of approval could be achieved.
FDA's attention to reducing approval times in general has produced very positive movement. In a review of 854 NDA applications during 1979 - 1986, Center for Drugs Deputy Director Gerald Meyer found an average approval time of 24.8 months, most of which was attributable to incomplete or inadequate submissions, which were withdrawn and then resubmitted. In a subset of 204 NDA applications, the total approval time was only 13.5 months. During 1984 and 1985, of 15 new chemical entities which were not approved by the FDA and which had to be resubmitted, 14 of the 15 were deficient in their clinical studies, 12 of the 15 had inadequate design of clinical trials, and 8 had tested in too few patients. The point which Meyer and other managers of the FDA have made, is that drug developers do not adequately design and prepare their submissions so that the product approval process can go through on the first attempt, without having to recycle to answer easily-identifiable questions. So FDA's principal suggestion for improvement of the process has been that the drug company submitters "do right things right". Doing the submission of drug data correctly on the first round requires experience, and the larger pharmaceutical companies tend to be better prepared and experienced for this submission process. This provides them with an advantage in the clearance time for approval of new drugs.

This discussion does not mean that smaller innovative drug companies which find an AIDS-related drug product and seek its approval by the FDA would be discriminated against. Approval in fact could be rapid. FDA's first NDA clearance for the AIDS
drug zidovudine was reviewed and approved within 108 days after the NDA was filed. IND's for AIDS related drugs are being reviewed within 5 days, and applications for treatment INDs are being reviewed within 15 to 30 days. So for the AIDS drug category, FDA views its internal workings as more than adequately able to adapt to the needs of the sudden crisis in AIDS products.

However, critics continue to feel that the FDA could do more to adapt its thinking on drugs in general to the needs of the AIDS population. This would probably require a legislative action to alter the effectiveness standard from a plural "adequate and well controlled studies" to some form of conditional efficacy approval for marketing with limited controls, and a easily-withdrawn approval in the event of discovery of adverse reactions. The English system of drug product approval, managed by the Committee for Proprietary Medicinal Products (CPMP) is likely to approve the marketing of a new drug in Great Britain more rapidly than the same drug would be approved in the United States, but Britain also withdraws drugs from the market much more rapidly, if the products are found to have adverse reaction experience levels which were not anticipated by the sponsor at the time of the product's submission to the government for approval.

The trade-off involved in permitting such a conditional product approval is that a drug marker has a larger investment in the marketed drug, which can be lost if the drug is withdrawn much more rapidly and easily. Conversely, the public might believe that it is subjected to inadequately tested drugs because of
governmental inactivity. The trade-offs are a matter of great social controversy. In the atmosphere surrounding the medical prognosis for HIV-infected persons, this conflict of competing values becomes even more difficult to balance.
CHAPTER 15
POST-APPROVAL CONTROL ON DRUGS

Section 15.1 - Timing of Approval and Sale

At some time between 6 and 36 months after the NDA is filed, the new AIDS drug is likely to be approved (if it has not been withdrawn by the sponsor). Approval of the NDA is not the last step of FDA involvement with the product. On the contrary, it will often seem like FDA has just begun to get involved. The regulatory agency approval takes the form of a letter which specifies that the particular drug and the particular advertising or labelling claims are acceptable to the FDA. The label which was approved by the FDA and the accompanying leaflets, instructional materials and the like (cumulatively described as labelling) are placed on the public file. The FDA lists the drug in a monthly report of new drugs approved by the FDA, which is widely circulated by the National Technical Information Service to interested persons and subscribers. Anyone who wishes can ask FDA for copies of the approval letter, label, a summary of safety and effectiveness test results, and copies of the FDA reviewers' reports on the approved drug.

After the product approval letter has been sent, sale normally begins immediately, since the manufacturer will have prepared a stockpile of manufactured drugs awaiting the approval.
letter. FDA, in most cases, has already approved the contents of advertising for the first wave of pharmaceutical advertising, before the final approval letter is issued.

Sale of the product should not begin before the FDA's approval is received, because this would be a violation of the law and would subject the manufacturer to not only a challenge for illegal sale of an unapproved drug, but on a more practical basis, would jeopardize its investment in the NDA approval process. FDA staff personnel associated with the drug approval process would probably react badly to news that the product manufacturer had not waited for their approval, but had begun to distribute the product without awaiting its acceptance through the appropriate channels. The loss of FDA final approval, or its substantial delay, is usually enough of a deterrent to cause drug companies to avoid any sale of the product prior to the FDA's issuance of the approval letter. (Treatment IND use of the drug may continue, however.)

As with any complex, multi-faceted government approval, of course, there may be a last minute snag. There might be an FDA review of advertising which seeks to eliminate one of the drug's major selling claims. The last minute negotiation which goes on prior to a drug's approval is often one sided, with the FDA's staff persons who are interested in making a change or limitation in the drug very eager to make the change while the sponsor is very eager to get approval, and very willing to make necessary changes in order to win that approval.
Section 15.2 - Establishing Medicare Payment Status

Although the FDA has approved a particular drug for the marketplace, it may be necessary for the manufacturer to also negotiate with the federal agency responsible for federal Medicare and Medicaid funding programs. The Health Care Financing Administration controls the set of reimbursable hospital and outpatient service activities. Private insurers who reimburse for drug costs often follow HCFA's lead for new medical product cost reimbursement. If the HCFA does not accept the validity of this drug for the patient-related conditions to which it is indicated, the product will not do as well as the manufacturer wishes because hospitals will not use a product for which Medicare will not pay.

For example, a product which was approved by the FDA and comes onto the market at $200 per 3-day course of therapy may have difficulty winning the approval of the HCFA for governmental health program reimbursement if the HCFA views a hospital treatment of that particular illness as more appropriately being done with a generic, "old" drug of $30 per 3-day treatment.

The substitution of therapeutically equivalent drugs is a matter of hot controversy. This controversy is discussed in the succeeding chapter. It should be noted at this point, simply, that the HCFA acceptance of a particular new drug may be vital to the manufacturer's recouping its significant investment in drug research and approval. More experienced firms have factored into their time schedule the need for both NDA and HCFA concurrences of new AIDS drugs.
Section 15.3 - Reporting Adverse Experiences with Approved Drugs

Drugs which are toxic enough to kill the elusive HIV virus and the infections symptomatic of AIDS will be harsh. They will inevitably have side effects. Acceptance of the risks of adverse effects from use of the AIDS-related drug, first by FDA and later by the AIDS patient, requires accurate reporting of user experiences. A risk must be understood before FDA can deem it to be acceptable.

FDA had some weaknesses in its reporting channels. The best way to get the attention of drug companies to encourage their rapid reporting of serious adverse effects with marketed drugs, was, in the opinion of the Food and Drug Administration, to bring criminal prosecutions. And so in the early 1980s, the FDA brought criminal indictments against two major pharmaceutical manufacturing firms. (AIDS drugs were not involved.) The consequence of these indictments was to stimulate manufacturers' obedience to the FDA's desire to get rapid reports of serious adverse reactions of deaths associated with (but not yet proven to be) the results of ingestion of a newly-approved drug.

In this section, definitions are all-important. Reporting of drug adverse reactions continues even after the new drug product has been approved for years, and can apply to products which do not have FDA prior approval because they are "old drugs" (so long as they are prescription medications). These reporting requirements do not apply to over-the-counter drugs, but will apply to all AIDS-related prescription drugs. The definition of greatest
interest to the patient population is that the manufacturer must report unexpected reactions which are serious because they are life threatening, disabling, required hospitalization, or required prescription drug therapy for the patient. Some reactions are unexpected because they are not listed in the FDA-approved current labelling for the drug. And, in some cases, the FDA can calculate that the rate of occurrence of an adverse reaction or experience is greater in frequency than was anticipated. After the appropriate adjustment for drug exposure, this increased frequency could signal a need for the FDA to examine whether continued approval of the drug is appropriate, or whether seriously labelling changes are needed.

The format used by the FDA to collect adverse experience reports after product approval is predominantly the "periodic report". After approval, there must be an adverse drug experience report filed at least quarterly for the first three years, and then annually thereafter. FDA examines the drug's annual report to determine whether changes in product labelling or other regulatory activity may be necessary, even after the product has already been approved. If the manufacturer has performed clinical studies after product approval, or has found adverse reaction reports in the scientific literature, or in foreign marketing experience, then the manufacturer has a responsibility to notify FDA of this adverse information.

The most crucial adverse reaction reporting is that of a "15-day alert" report. These reports are filed with the FDA
whenever a new drug's adverse experiences are both serious and unexpected, regardless of the source of that information. These events must be reported as soon as possible, but within 15 working days of the company's initial receipt of the information. FDA standard forms must be used in this reporting. The FDA is insistent that these alert report formats and reporting schedules be used so that a particular observed adverse reaction does not become "lost in the system", but receives the appropriate level of attention from the drug regulatory official who have reviewed the original drug approval. In the FDA's expectations, alert reports will have the highest priority for drug reviewers. Changes that may be needed for the drug label will be ordered promptly when it is observed that a marketed drug has failed to perform as expected, or has had a serious adverse reaction occur.

The responsibility of the manufacturer to report adverse drug events is crucial to the FDA's ability to monitor the post-approval status of the drug product. FDA has made it clear in speeches, letters, and guidelines, that adverse drug experience information MUST be reported to the FDA in the time frame specified by these regulations (quarterly, annually, or on a 15-day basis).

For the person interested in an AIDS drug, rapid approval by FDA may be a two-edged sword. Rapid approval may mean that the product reaches the market and can be administered much more widely, much more rapidly than a typical therapeutic drug for a traditional illness. But the traditional illness drug is less likely to have close scrutiny of its periodic reports than is the
AIDS drug. FDA keeps close watch on the rapid "fast-track" drugs to make certain that its own decision to approve these drugs cannot be attacked as precipitous in hindsight. That is, FDA will watch the adverse reactions to determine whether the FDA will be subject to criticism for having rapidly approved a product which later is discovered to have some adverse effects in patients to whom the marketed AIDS-related drug is administered. FDA is also concerned, of course, that it should be able to react rapidly when a new pattern of adverse reactions is discovered. FDA wants to be able to rapidly order the change of label instructions, the reduction of dosage, the limitation of prescribing a drug, or other means by which the product may be reduced in its ability to reproduce this adverse effect in other patients. By knowing of the adverse reaction quickly, and by being able to assess its impact, the FDA hopes that the ill effect which any one patient experienced will not be repeated.

The benefit of adverse drug experience reporting for the HIV-infected person, is that the FDA is less likely to hold off on the approval of the drug until it is certain that all the experiences have been examined. FDA is, on the other hand, more rapidly able to respond and control drugs which offer some promise, and which come on the market with promise, if these drugs develop adverse reactions more serious or more frequent than were anticipated. The patients who are being treated with that approved drug might be maintained on the product after the additional FDA warning, or may be moved to another pharmaceutical.
Section 15.4 - Controls on Prescribing Certain Drugs

After the FDA has approved an AIDS-related drug for marketing, another potential delay point comes into play. The AIDS-related drug may not be able to get onto the market if it is believed to be potentially habit-forming. A habit-forming drug may be a very mild sedative or a serious narcotic drug. If the product is habit-forming, the FDA notifies the Drug Enforcement Administration and the DEA employs its formal scheduling process under the Controlled Substances Act to place the drug product on one of the five control schedules.

The purpose of the Controlled Substances Act is to limit access to drugs which may be habit-forming, and to tightly control those physicians and pharmacies who may be involved with the dispensing of controlled substances. Those prescription drugs which are capable of abuse by creating a dependency problem are appropriately dealt with by DEA. That agency holds scheduling hearings after FDA approves a drug, which necessarily impose limits on the sale of the new drug. The habit-forming nature of the drug means that the DEA will control its accessibility to patients, and by doing so will indirectly increase the price of its availability. If an HIV-infected person requires a pain-killer, for example, the pain killer is likely to be on a schedule of drugs under the Controlled Substances Act, and the dispensing of that pain-killer may be limited to certain physicians and pharmacists.
The police-oriented control function of the DEA is more difficult for manufacturers to overcome than the regulatory controls of the scientifically-oriented FDA reviewers. Drug developers can expect that approval of a habit-forming drug for FDA's purposes will be only the beginning of a 6-to-18 month period, before a final scheduling order from the DEA which would permit the habit-forming drug to be marketed.
CHAPTER 16
FINANCIAL ASPECTS OF DRUG APPROVAL

Section 16.1 - Drug Research is a Profit-Centered Activity

With the exception of the National Institute of Health, virtually all of the major clinical research studies done in the United States are done for profit by pharmaceutical development companies or their agents. The process of getting a new drug approved is expensive, far beyond the means of virtually any non-profit organization. The profit motive also improves the orientation toward timely processing of the NDA since there is a strong financial incentive for the manufacturer to develop and expedite the clearance of factual data concerning the drug.

From the point of view of the AIDS patient, it is a mixed blessing to have the private sector so thoroughly involved, since some aspects of the private sector involvement are not welcomed, when their rate of return causes a significantly higher cost per dose of an AIDS-related medication. On the other hand, it is probable that the high level of quality research work being done is attributable to the profit motives of the research companies, each competing for an opportunity to market the first of the effective drugs to be available for HIV-infected persons. Therefore, the speed of the research effort is likely to be greater with the profit orientation of the drug development process.
This chapter addresses the financial aspects of drug approval, not because they are central to the Food and Drug Administration decision on new products, but because it is important that the reader understand the motivation and incentive which are an integral part of the decision on which drugs to develop, at which speed, and for which indications. These financial aspects impact on the system of drug approval, but generally do not taint the FDA's approval process for drugs. It is very rare that financial incentives affect the actual FDA approval of the drug, and with its strong ethical and conflict of interest controls the FDA itself is rarely to be affected by the economic aspects of drug approvability.

Section 16.2 - Drug Product Pricing

The subject of pricing for AIDS-related drugs have been extremely controversial in light of the cost to patients of the first approved AIDS drug, Zidovudine ("AZT"). The economic aspects of recovering drug costs are relatively simple. Because so few drug products work out economically, and even fewer reach approved-drug status, manufacturers have a significant financial incentive to recover costs on those successful products that actually come to market. These cost recoveries must include the reality that a product's life cycle will be less than that product's legally-protected patent life. Within three to five years, a newer version of the product developed by a competitor is likely to take away some of the market enjoyed by the pioneering drug. Some drugs defy
these age presumptions; Tagamet, for example, is a major seller as a therapeutic agent for ulcers, and has enjoyed a strong market share since its inception, although later entry of competing products has reduced its relative position from one of dominance to one of significant market share.

In the AIDS-related drug category, because of the large amount of research being devoted to AIDS, it is extremely likely that product life cycles will be one to four years, rather than 3 to 7 years, before replacement by a less toxic or more effective alternative product. Since the expectation of evolutionary product improvements and new product entry is so clear, pricing of the drug product must recover that large research and development risk investment during a relatively short period of product dominance in the marketplace. This means that the drug's cost per dose will be significant. Cost of the AIDS-related drug will then be important in treatment plans, particularly since physicians may try several different kinds of pharmaceutical products upon the same patient in order to determine whether the patient is better protected by one anti-viral or another.

FDA's interest in approving new drugs is totally unaffected by the relative price of the two products. However, the appearance of a potential competitor in the FDA pipeline is likely to induce the manufacturer of the product which already on the market, to increase it price. The increase in price enables the original manufacturer to recoup more of the cost of the product, in the shorter life span remaining before the newer
product entry comes on to the market to the detriment of the first entrant into that market.

The ultimate meaning of this pricing process is that the price of AIDS-related drugs is likely to become higher and higher, amid the several types of economic and governmental pressure for drug product improvement, replacement, and new product development. Over the long term, it is likely that drugs for HIV-infected persons will still be developed by the private sector of pharmaceutical developing companies, but that the cost of product development will probably be less capable of efficient recovery by the normal means. There will eventually be some form of patient subsidy, some expansion of orphan drug subsidies for product development, or a national wide system (similar to that offered in the California State Legislation) to economically subsidize the development of the needed AIDS drugs or vaccines.

Although the cost of the raw materials needed for the AIDS drug or vaccine are quite high compared to those of other well-established drugs, the markup added to the cost of raw materials is composed of research and development and administrative overhead costs, products liability insurance (a not insubstantial expense), drug promotion costs (to expand knowledge of the benefits of the drug among physicians and patients) and profit (to win analysts and shareholders' support for the expensive gamble of going after such a high-risk product development area). If the federal system were to establish subsidies, these subsidies would probably take the form of financial inducements for the
manufacturing community to develop the AIDS-related vaccine or pharmaceutical, with the government assuring a market by guaranteeing its purchase. This type of approach has been developed in California, where that state government through one of its health agencies’ would purchase enough output of the product sufficient to produce a fair rate of return for the manufacturer. Such market-creating policies are designed to stimulate manufacturers to generate the additional product research and development investment needed to enter the AIDS-related drug market place.

An additional pricing factor is licensing agreements. To obtain rights to develop a federal laboratory’s invention, a drug company may agree to limit its profit from marketing the drug. How and under what terms such contracts may develop for AIDS-related drug products will be an important area for future policy attention. Licensing could actually raise prices, if the invention is licensed from a profit-oriented commercial licensor.

Section 16.3 - Patents

The patent system, established directly in the U.S. Constitution, now provides by implementing statute a 17-year exclusive right to inventions which meet the legal prerequisites for patentability. The United States Patent and Trademark Office, an agency of the Department of Commerce, examines newly invented drug and vaccine products, determines whether they meet the requirements for a patent issuance, such as “novelty” of the
invention, and grants exclusive rights to the use of the invention during the life of the patent term. In this respect, AIDS-related drug patents are no different than those for virtually every other invented product for which patentability is established.

What is unusual about the drug patents, however, is that the process of NDA approval reduces their value from 17 years to an effective life of perhaps 9 to 12 years, depending on the time period consumed by product regulatory requirements such as the investigational new drug exemption requirements.

Under the 1984 amendments to the Food Drug and Cosmetic Act, manufacturers who win approval of an NDA or win licenses for a new vaccine which also receives new drug clearance, can obtain an extension of their patent term which corresponds with the time actually consumed in the FDA review of the product, or the FDA-required IND testing. This patent term restoration provision allows the drug manufacturer an opportunity to receive a net amount of time which is equivalent to that which a consumer product or other traditional products might enjoy over the lifetime of a particular patent. Because of this patent term restoration legislation in 1984, the patent lives of several drugs have been extended beyond their original expiration date. Once the patent expires, other manufacturers (who have cleared their products with the FDA) are free to manufacture the drug without infringing the original patent of the pioneer manufacturer.
Section 16.4 - Exclusivity Through FDA Approval

Under the 1984 Waxman-Hatch Amendments to the Food, Drug, and Cosmetic Act, there is a parallel system of exclusivity beyond the availability of a patent. The manufacturer who first comes to the FDA for the approval of the chemical entity can obtain an exclusive right of NDA approval, regardless of patent status, for a defined period of years. The FDA grants this exclusivity as another means of incentives for the manufacturer to seek and obtain FDA clearance.

The exclusivity periods depend upon the timeframe of FDA's drug approval process. The exclusivity periods were established with a sliding scale of years so that manufacturers whose products require a considerable amount of clinical testing could obtain exclusive rights to NDA approval for that period of time. A manufacturer who does not obtain this FDA exclusivity will not be able to enjoy the marketplace benefits that flow from barring a later manufacturer from the FDA approval process, but the first manufacturer may still obtain exclusive legal rights by becoming the first to obtain a patent under the patent law system.

In the case of an AIDS-related drug, FDA exclusivity would often apply if the manufacturer of an existing anti-viral drug won FDA's approval of the supplemental new drug application for the indication which is related to the HIV infection. A traditional cancer drug, for example, when an additional test program is completed, might be granted a supplemental new drug application for Kaposi's Sarcoma. When that occurs, the
manufacturer who has obtained the supplemental NDA through the filing of clinical studies is granted an additional three years of exclusive rights, and subsequent manufacturers seeking FDA approval of their respective products will not be granted supplemental NDAs for that same indication. The other manufacturers, of course, may generate additional data for their own, different new drug applications, and may obtain approval. However, a second or generic maker of the same chemical entity for that newly-approved indication would find its way blocked for a 3-year period of FDA approval exclusivity. This is an important aspect in the race to the marketplace, since the manufacturers of existing drugs which prove beneficial for an AIDS-related indication are given a strong financial incentive to be the first product approved through the supplemental NDA process. From the point of view of the AIDS patient, this race for FDA exclusivity is a net benefit. Manufacturers of existing drugs which have a profile of safety or a degree of public experience and acceptance may be able to develop additional clinical data regarding the HIV infection prevention or treatment aspects of such a product. When this occurs, the exclusivity provisions of the 1984 Act help the search for an AIDS-related drug by providing an economic period of exclusivity which might not be available under the patent law system. If the patent law system and FDA exclusivity for new drugs alone were applied, then as a consequence, there would be little incentive to seek out the use of existing safe products for possible testing and use against the AIDS/HIV injection. Overall, the FDA exclusivity
provisions for a particular chemical provide a beneficial stimulus to the AIDS-related drug research and development process.

The economic downside of FDA exclusivity is that when the life cycle of the product can be no more than three years, because of the appearance of competition after that point, the manufacturer of the product which now has an AIDS indication approved for it may seek to maximize its financial return during the three year period of FDA exclusivity. The net result of such a decision may mean that the price per dose of the product before its AIDS indication may be low, but the price after approval and then for the next three years will be significantly higher in light of the urgent demand. The desire of the manufacturer to quickly recover its research and development costs and perhaps profits by which to finance further research may thus naturally clash with the AIDS patients' perspective, resulting in an exchange of charges of price-gouging and exploitation versus claims of insufficient financial returns to finance the next generation of AIDS-related drug research.

Section 16.5 - Orphan Products Act

The concept of the Orphan Product Act legislation, first adopted in 1982 and subsequently amended three times, is very simple. Drug research can provide a benefit to smaller numbers of patients who have relatively rare diseases, but only if the government provides an economic stimulus for the development of such products. Otherwise, these products are unlikely to be
developed, for they would be considered economic "orphans" in the marketplace of product development, which is oriented to much larger prospective patient markets. The Orphan Products Act affords the manufacturer of a new drug, medical device or special nutritional food product, two forms of governmental assistance, and one form of product protection.

The forms of product assistance offered under the Orphan Products Act are financial aid from the government for the development of clinical study information concerning the effectiveness and safety of an "orphaned" new drug. In addition, the government offers tax advantages in the form of tax credits for those manufacturers who expend funds for clinical research work upon orphan drugs IND development stages. The Orphan Products Act assistance is not unlimited, but it can be the keystone of product development efforts for products which would otherwise be marginal or negative producers of profit for a drug developing company.

The orphan products category includes products for certain of the AIDS-related symptoms, which symptoms occur very rarely. All these medical symptoms associated with the AIDS clinical definition are rare, but the growth of concern about the AIDS-related drug products has focused more attention upon the point at which a product is no longer to be considered an orphan, but may become a major financial producer of profit for a manufacturing company. Under legislation approved in 1988, drug products lose their "orphan" status if the FDA determines that they no longer qualify or if their "orphan" status is not appropriate.
The special importance of the Orphan Products Act to HIV-infected persons is that as symptoms are defined in classes of patients, these symptoms are frequently unusual enough to be beyond the reach of traditional therapeutic products. In order to service the relatively small number of patients who have these rather unusual symptoms, the Orphan Products Act provides a useful economic incentive. Cumulatively, AIDS-related illnesses can be treated by a variety of existing drug products, but if the manufacturers of those products wish to develop an AIDS-specific indication, these manufacturers should consider whether or not the Orphan Products Act's assistance programs would benefit their research and development efforts for the AIDS-related indication.

Section 16.6 - Effects of the 1988 Catastrophic Medicare Bill

In 1988, Congress adopted a Medicare reform bill which provides, for the first time, for the payment of outpatient drugs which are purchased by or for the Medicare patient. The federal government's role as purchaser of these drugs will, by the mid-1990's, make the federal government the primary purchaser of more than one-third of all pharmaceuticals sold in the United States. This new policy enhances the federal government's already commanding position as the purchaser of medications for federal employees and retirees as well as military employees and veterans. Cumulatively, that purchasing power will have a significant economic impact on the ability of AIDS-related drug developers to obtain compensation from the federal government for the economic
risk incurred in the development of new AIDS-related drugs. For example, the federal government may choose to provide a 15% rate of return on normal pharmaceutical sales, but with the federal government's enormous purchasing power, conceivably a much lower rate of return will be established in the marketplace on sales made to or reimbursed by the federal government.

Experts have studied in detail the long-term consequences of having the federal government as the principal purchaser of pharmaceutical products. They have speculated that, in the long term, concentration of drug companies will result in a relative handful of major manufacturing firms, which can afford to try new and experimental therapies, and a larger number of generic drug firms which make products without doing virtually any research of their own. The number of mid-level drug firms between these two categories will decline rapidly during the 1990's, it is predicted, because the costs of research and regulatory approval will have increased so high that, if it were to be displayed on a graph, the upward curve of product development costs intersects with the downward movement of pharmaceutical prices for governmental purchases to the extent that fewer companies will be able to take the chance of having a non-breakthrough drug. Those larger companies can sustain growth, and the development of further drugs from the profits of the patented, and therefore exclusive, new "cash cows" from which the research budget can be internally financed.
If these predictions by financial analysts are correct, and the number of drug companies declines, those which remain will have a stronger financial base and can use their financial position effectively to develop research in the AIDS categories.
CHAPTER 17

VACCINES AND LICENSING

Section 17.1 - How Vaccines are Developed

A "vaccine" is a broad general term for a biologically-derived organism, which has a beneficial impact in the body such as destroying an unwanted virus. The development of the vaccine is basically the search among many biologically-derived components for an organism which will not be harmful to the body, but which will produce a body's natural defenses against the harmful virus.

A vaccine may be developed from biotechnology, such as the recombinant DNA technologies. A conventional type of vaccine is made from a weakened or killed version of the virus or the bacteria which originally caused that illness. Scientists weaken or destroy the growth factor in the virus or bacteria, but leave enough activity so as to stimulate the body's immune system. With the weakened or killed virus present in the vaccine, the body is stimulated to produce antibodies to the disease, but the body does not go further (as it would with a live virus) to develop the actual disease. The advantage of using a recombinant DNA or similar technique in biotechnology is that the biotechnology product duplicates the appearance of the virus particle within the blood stream, "tricking" the body and stimulating the immune system.
system, but does not have any of the activity which could make the virus dangerous in the body. So the ideal vaccine for the HIV virus would be one which the body defenses assume to be the live virus, but which is not the actual virus. Such a vaccine would stimulate the body's natural defenses. By using the biotechnology product instead of the weakened or killed version of the live HIV virus, the body receives the stimulation effect without receiving the risk of development of the actual illness.

The challenge for the vaccine developer, of course, is to consistently produce a product which the body believes to be a harmful pathogenic bacteria of a virus, but which is in fact not harmful to the body. This is a considerable construction challenge for the microbiologist, who is developing the vaccine. When the vaccine search is successful, after examining thousands of potential combinations, the microbiologist must then evaluate how the product can be purified and consistently manufactured to the same level of quality and precision.

The process of regulating vaccines is older than the process of regulating drug products. Vaccines and other blood-derived or human organism-derived products have been regulated since the 1902 Virus-Serum-Toxin Act. After major revisions to this law in 1944, vaccines today are among the most highly regulated products in commercial distribution. FDA specifically approves each batch of vaccines produced, by licensing the establishments at which vaccines are made. Therefore, there is a
specific approval of manufactured products and of the factory, in addition to the approval of the product itself.

FDA's vaccine regulatory program requires that the FDA accept the product after reviewing its test results and that subsequent batches and manufacturing sites be specifically approved.

Section 17.2 - The Product License System

The approach to vaccine approval is significantly different than the approach to drug approval. The Food and Drug Administration's Center for Biologics Evaluation and Review and the National Institute of Health are much more closely aligned with the research process, encouraging new vaccine development, than are their colleagues in the pharmaceutical drug approval offices. The FDA approval offices for vaccines become more closely involved because of the importance of vaccine development and the biologics group's traditional joint mission of regulating and stimulating vaccine projects. The role of the FDA toward vaccine development is underscored by the fact that the current head of the Center for Biologics Evaluation and review, FDA veteran Dr. Paul Parkman, was the discoverer of the German Measles vaccine. Parkman, a dedicated microbiologist-physician, has committed many of the resources of his Center toward the development of an AIDS vaccine. These resources are being spent to assist in development, design, and execution of clinical trials, as well as to review the
The human safety testing of vaccines is more complex than the testing of pharmaceutical products. The persons selected for the clinical tests must be more thoroughly screened for the presence of any existing antibodies before the experimental vaccine is introduced into their bodies for the purpose of creating new antibodies. That is, if the patient's blood already carries the natural defenses against HIV virus, then he or she should not be used as one of the test subjects for the experimental vaccine. FDA also works very closely with its Advisory Committee on Immunization Practices, which is the principal advisory body regarding vaccine matters. The FDA's approach to the testing efforts involves closer cooperative work with the Centers for Disease Control and the National Institute of Health staffs which have research-related responsibilities for vaccine development in this category.

The large-scale clinical trials of the experimental vaccine may be more difficult to conduct than the comparable efficacy experimentation with the pharmaceutical drug. The protocol design will be worked much more closely with government researchers at the time of development of the protocol, since government has both a promotional and a regulatory review function for these products.
A significant difficulty for a vaccine development will be the matter of the patients' informed consent. This informed consent is especially difficult where the purpose of the clinical study is to develop an HIV-antibody in the person. The development of this HIV-antibody in the person's blood stream as a result of the vaccine clinical experiment has a long-lasting negative effect upon that person's ability to deal with the matter of HIV-infection. A person who is not HIV-infected must be recruited for the early stage clinical trials of the experimental HIV-vaccine. However, the purpose of the experimental vaccine is to produce the HIV-antibodies needed to ward off the HIV-infection in the future. The paradox involved in this informed consent is that the individual who is healthy and remains healthy after being successfully tested with the experimental vaccine will, in the future, be incorrectly identified as HIV-infected because the HIV-antibody will show up in the blood stream.

The result of this paradox is that in the future, the normal HIV-antibody tests for AIDS will incorrectly judge the status of individual persons who participated in the AIDS experimental vaccine clinical trials. Participants in the trials will have to get special informed consent before they expose themselves to the experimental vaccine, not necessarily because of the risk from the vaccine, but because of the future stigma which might attach to having tested positive in an HIV screening test for the presence of antibodies. If a group of 100 healthy persons is recruited in 1992 for the testing of an AIDS vaccine, and none of
them are found positive in the blood tests conducted to determine the presence of the HIV-antibodies, then the issues of personal fear, employment discrimination and non-insurability problems come to these volunteers as soon as the experimental vaccine produces HIV-antibodies in their blood streams. Future HIV-antibody tests are unlikely to be able to differentiate an infected person from a past experimental vaccine test volunteer. To deal with this problem, participants in experimental vaccine clinical trials in the private sector will probably be given some form of permanent identification, similar to the NIH certificates, to spare them from the consequences of being identified erroneously as HIV-positive.

Section 17.4 - Special Concerns with the AIDS Vaccine

Because "live" HIV retrovirus can develop into fatal symptoms, in many cases of infected persons reviewed to date, it is imperative that there be no mistakes in the processing of a "killed" or attenuated "weakened" strain of the virus used in manufacture of the vaccine. It will be important that the version of the AIDS vaccine which is licensed would NOT have the potential to actually give the HIV infection to a person who seeks the benefits of the vaccine.

In order to have this beneficial vaccine without the risk of errors in the processing of "killed" or weakened vaccine forms, it is probable that the vaccine to be licensed will be developed from biotechnology. The biotechnology options to be used are essentially designed to duplicate the structure of the HIV virus.
proteins within the body, triggering the body's defenses against that virus, but biotechnology can permit the scientists to "trick" the body's systems. Thus the body, although it believes it is being attacked by the HIV retrovirus, is actually receiving the vaccine, a harmless particle which is biotechnologically altered to resemble the form of the virus. Therefore, if the scientists can develop the appropriate design, society can have the benefit of a vaccine without the negative aspects of a potential failure in the "killed" virus process.

The presence of a vaccine for AIDS does not substitute for the continuing efforts for proper education and avoidance of high-risk behavior patterns. These activities must continue, because the vaccine is not yet established as a permanent form of avoidance of the virus. If the virus, or a new strain, were not adequately prevented from growing in the body, then the vaccine would need to be re-administered periodically, or the vaccine could be presumed adequate even though the individual had been exposed to a different strain of the virus. The ideal would be a one-time vaccine injection, which addresses all of the known strains of HIV and renders the person impervious to HIV infection for many years in the future. That wonderful ideal of vaccine administration may not ripen into reality for quite a number of years.

The vaccine manufacturing cycle with biotechnology materials is much more technologically complex, but likely to be more "pure" in the outcome, than the production of traditional vaccines which are derived directly from the active virus of the
disease itself. The unanswered questions about the protein, the retrovirus, the form of administration, changes to the virus protein, etc., make it difficult to predict how rapidly an AIDS vaccine can be developed. The biotechnology work remains crucial to the development of the model upon which the design of the vaccine can be premised. However, experts have warned against false hope, since there are so many unanswered questions about the viral design and these limitations of knowledge limit the ability to rapidly transfer from an identifiable disease to an identified vaccine.

The FDA will insist that the information on labelling given to professionals about a vaccine describe the potential adverse reactions and the probability of ineffectiveness of the vaccine for a patient. The FDA may regard the vaccine for HIV infected persons as a unique situation, since no other product like it will exist at the time of the approval of the vaccine, and demand for the product is likely to be extraordinary. This means that the FDA will be devoting attention to the purity with which the product can be made from these biotechnologically derived components. If the manufacturer can determine on the basis of clinical studies the percentage of the antibodies which are likely to be created, or can otherwise put a quantitative measure of success around the predicted effect of the vaccine, then the FDA may be satisfied.

For products liability reasons, the manufacturer will have an incentive to hold down the claimed efficacy rate, the
percentage of patients referenced in the labelling as those likely to be benefited from the vaccine. The strong possibility exists that the FDA may wish to hold off on the approval of the vaccine until the percentage of persons actually rendered immune by the vaccine is shown to be statistically significant and large enough to warrant the attendant risks. This will conflict with the manufacturer's economic and products liability incentive to reduce the percentage of effectiveness which the manufacturer claims for its vaccine. The larger the percentage effectiveness of the vaccine which is claimed, the higher the exposure of the manufacturer if that percentage prediction proves to be incorrect as the vaccine is eventually distributed and actually administered. Because some recipients will not become immune, and some may sue from within that group, the manufacturer needs to approach that percentage figure on labeling with an attitude of great caution. Waivers and release forms may be exceedingly detailed.

Although the FDA will typically approve a second generic version of a pioneering pharmaceutical drug upon relatively little proof, there is not assurance that a "me-too" manufacturer of vaccines will be able to enjoy the same kind of liberal approach. FDA will typically require detailed information in support of the licensing of the particular product, the particular plant, and the particular company. If the manufacturer changes plants, or if a second manufacturer comes on to make the same product, then there will be a need for an additional specific license.
The vaccine field in the United States has not been crowded in recent years, because the high cost of products liability insurance has forced many companies out of the vaccine marketplace entirely. The manufacturing of a vaccine involves some inherent risks, but court cases and unsettled matters of tort law suggest that there are problems which need to be resolved before an AIDS vaccine can be considered a likelihood.

FDA may grant approval of an AIDS vaccine, which then cannot be marketed until the product liability insurance problems of the manufacturer are resolved. In a 1988 decision, the U.S. Supreme Court said that in certain rare cases, FDA could be liable along with the vaccine maker for an injurious product. These questions of vaccine experimentation, related to product insurance and products liability, are illustrations of problems caused in the civil justice systems as a result of deficiencies observed in drug and vaccine products. This is a sore spot in the interface between regulation and liability, which deserves to be resolved.
Chapter 18

Medical Devices

Section 18.1 - Introduction

Some of the most important new medical products which FDA approves for use in the struggle against AIDS are medical devices.

The law's distinction between a drug and a medical device is essentially a distinction between two forms of activity: a drug has some chemical activity in or on the body, such as by dissolving in the blood stream or penetrating the outer layer of skin, while a device includes all other medical-purpose products which do not work through chemical activity in or on the body, such as condoms, surgical masks, crutches, etc. If a product does not dissolve or interact chemically with the body (or if it interacts chemically only in the laboratory-type setting of a diagnostic kit outside of the body) then it is classified by FDA as a medical device.

As with all legal distinctions between two seemingly exclusive classes, FDA has found overlaps and confusion in a few areas of the definition. For example, test kits which detect HIV by using biological materials derived from human cells are regulated by the devices staff in coordination with the FDA Center for Biologics Evaluation and Research. An electrophoresis column, a complex machine for cleansing the blood outside of the body and recycling it into the blood stream, is a medical device but it
needs a special drug to make it effective. The machine and its components are approved as devices but before the drug can be used for this special indication, approval by the Center for Drug Evaluation and Research is required.

In practice, the FDA organizations cooperate to come to the most efficient regulation, with inevitable "turf battles" over the most complex of the mixed drug/device products. Once a definite status is known, the products follow distinctly different channels.

Medical device regulation was completely updated in 1976. It is improved over the drug system, which dates from 1962 and 1938. In general, an FDA approval of a medical device will be faster and simpler than the comparable approval of a new drug. Congress established two clearance methods, one premised on familiarity with the kind of device, and one premised on full safety and efficacy review as is done for drug products. Products which are relatively slight changes from the norm of existing medical devices come onto the market by notification of the safety and efficacy "substantial equivalence" of the new and the existing products. Products which fail this test of equivalence (and the number that fail is less than five percent of thousands of such notifications) will go through the full safety and efficacy support and review process, or not marketed at all. Several dozen products have gone through the full approval process for "premarket approval".
Medical devices will not cure AIDS, but they are important to the overall battle. First, medical devices can prevent transmission of the bodily fluids which carry HIV infection. Second, medical devices which provide laboratory diagnostic detection can help with earlier treatment and enhanced protection of others from the spread of that infection. Third, devices aid the survival of the actively ill patient, with catheters, dialysis, feeding tubes and blood analyzer machines.

A principal concern of the Center for Devices and Radiological Health of FDA is the effective decontamination of hospital and dental equipment used in the care of HIV-infected persons. FDA supervises the labeling of these products. For example, a medical device used for rectal biopsy in the detection of cancers, or a dental drill powered by water, may not be fully capable of being sterilized between uses of the device on patients. Bodily fluids may contaminate these reusable devices, or such common surgical devices as laser-tipped cutting catheters. The result would be passage of the contaminated fluids into the body of the next patient on whom the device is used.

FDA's ability to interrupt bad medical or dental practices is limited. FDA can require the device maker to put on the label the appropriate disinfecting instructions, if disinfection will work for this type of device. But FDA cannot be sure that dentists with water-driven drills actually run through a cleaning cycle adequate to clear the back flow of liquid.
suctioned from one patient, before that same equipment is used on another patient. FDA cannot adequately police what hospitals may do with delicate microsurgery devices whose disinfection may be complex and time-consuming when it is done properly. Nosocomial (hospital-based) infections with KIV are believed to be rare and there are no statistics on the number of AIDS cases attributable to medical device contamination with inadvertent HIV-infected bodily fluids. Incidentally, there is a separate federal group responsible for clearance of the disinfecting solutions themselves. The Office of Pesticide Programs of the Environmental protection Agency regulates the anti-AIDS claims which are permitted to be made on the labels of disinfecting solutions. FDA requires that the devices be disinfected when their potential for passage of HIV-infected bodily fluids is significant. So the FDA hopes that the user follows the device's label instructions, and for the actual disinfecting steps, EPA prescribes which steps in which sequence should be included on the label. Much of the actual responsibility for doing it right rests with the professional competence and integrity of the user.

Re-use of medical devices which were intended to be disposable might be a routine practice in some hospitals, contrary to the disposable product's package labeling, but until the hospital reuse causes a severe and traceable illness, the FDA may never know. The hospital's periodic auditors from Medicare or state hospital boards might find the medical device reuse problems much more readily than FDA could (and, in some cases, problems with
A separate area of medical device work is the detection kits. HIV detection using both the ELISA screening test and the Western Blot confirmatory test is believed to be close to 100% accurate. But screening tests will inevitably be the source of some number of false positive results. While FDA controls the labeling of these laboratory tests, it cannot routinely watch how the screening tests are conducted. By working with the biologics staff in a separate Center of the FDA, the medical devices staff seeks to assure that accurate screening tests will be available and that labeling will stimulate the user to follow directions to achieve accurate results.

The third category is treatment related medical devices for the HIV-infected person who shows active clinical symptoms. A booming area of treatment for blood disorders is the use of machines outside of the body which clean the blood. The extracorporeal electrophoresis machines are extremely complex. When combined with computer-driven blood analysis machines, these devices related to blood have the potential for errors in operator manipulation, in mechanical function or (the latest area of FDA attention) in software accuracy.

Sometimes the FDA decisions are not oriented to medical efficacy alone. When FDA denied the requests of test kit makers...
to market a home self-test kit for HIV, the denial was premised in part on concerns about accuracy and reproducibility of correct results. But FDA was more concerned that the kit user needs sensitive counseling in order to deal with positive HIV results. The tests which are positive but inaccurate must be verified through the lab-only Western Blot method. The tests which are positive and accurate should lead into a counseling session advising the test subject person what he or she should do next, now that he or she has been infected. Professional intervention might not be sought if there is no involvement of the medical community in the user's purchase and use decision making.

These are just a few of the product illustrations of HIV-related medical device activities in FDA's Center for Devices and Radiological Health. It is ultimately likely that FDA devices regulators, working with drug and pesticide regulation groups, will set the world's highest quality standards for the products which detect, prevent and mitigate the effects of HIV infection.

Section 18.3 - The Medical Device Approval Process

A very small number of medical devices have completed the full device premarket approval process, but many thousands have come onto the market after a short notification period. The full "premarket approval" (PMAA) process takes considerable time, as does the comparable new drug approval. It can be predicted that breakthrough scientific advances which come in the form of medical devices for AIDS mitigation or HIV infection prevention will have
to proceed through full approval, but they will perhaps go through the approval process even faster than those devices that have gone through the full approval process to date. The rapid fast-tracking system seen in drug approvals is somewhat less likely to occur for devices, because the device system does not have such a backlog of pending applications as does the drugs review group, and the degree of attention for the special AIDS products is likely to be great.

This chapter will separately consider the notifications of "substantially equivalent" devices and the full premarket approval of the truly new, innovative devices.

**Section 18.4 - Device Approval a- "Substantially Equivalent"

A new version of an existing medical device does not have to establish that it is safe or effective, but only that the new version is "substantially equivalent" to the pioneer.

The system of equivalence review is known as the "510(k) notification process", after the section of the 1976 amendments which permit products to be marketed on the basis of the rapid equivalence reviews. Congress gave FDA a negative option, an option to challenge a claim of substantial equivalence with the negative determination that the new version is less safe or effective, or "not substantially equivalent, in that the product is so novel that it has no real pioneer to which to be compared and thus cannot be "equivalent".

Definition of the equivalent status begins with identifying the base point to which the device is compared.
catheter or condom is compared to the closest possible similar product now on the market. If that pioneer is a device marketed before May 28, 1976, it is a true historic pioneer because it predated the 1976 amendments. If the pioneer and the new product each came onto the market after 1976, FDA could decide to treat the later device as an inadequate predicate for acceptance of the new version. Current attitudes of the FDA staff seem to allow the products marketed after 1976 to be readily used as the premise for a newly developed and "substantially equivalent" device.

When a device chooses to promote its special AIDS or HIV features, and the pioneer product did not do so, FDA may call into question the equivalence assertions. A catheter tube with a plastic developed in 1975 may be cited as the pioneer model for a subsequent device maker's stronger plastic catheter in 1990, for example. But FDA may balk at the 1990 product's claim that it is "specially formulated for avoidance of contamination in treatment of AIDS patients", a claim of benefit which the pioneer never asserted. FDA may use its negative option and demand proof, through the full review of a premarket application, that the device's effectiveness for AIDS patients was established by well-controlled clinical studies in catheterized AIDS patients.

To sum up, many medical device changes move easily through the regulatory screening process because they are not significantly different from earlier products to which their effectiveness and safety is "equivalent". Those which FDA doubts are effective, or those which make claims of AIDS effectiveness
beyond the claims made for the pioneer product, may have to go through the full review process described in the following section.

Section 18.5 -- Premarket Approvals for Medical Devices

FDA may require the manufacturer of a medical device to prove that it will be safe and effective. In order to accomplish this objective, the manufacturer goes through a procedure which is very much like the new drug application (NDA) process. The final result is a specific order by FDA approving the device and its labeling, for a specific indication. The product goes onto the market and subsequent changes are cleared by FDA as supplemental approvals.

For a device that bears AIDS related labels, the effectiveness testing issues may be very, very difficult. A new condom material, for example, would not be easily tested among sexually active persons who are known to be HIV-positive. Patients on kidney dialysis or dental patients who are presented with "informed consent" documentation may not wish to experiment at the risk of contracting HIV infection. But HIV detection kits for use in the clinical laboratory would be readily checked by "blind" samples with and without the HIV antibodies. Under the 1976 legislation, FDA can accept effectiveness data other than full clinical comparative studies where the substitute delivers adequate information.

When the new device claims effectiveness against the HIV infection as a barrier device, for example, the durability of the
materials will be important. FDA wants to know that consistent manufacturing quality will deliver the same level of barrier protection across all lots of the product.

New AIDS-related claims for existing devices are likely to require premarket approval if the changes are remarkably different from past uses and past labeling claims. A general purpose bandage is a device, but a bandage which claims to prevent HIV infection will require substantiation through safety and efficacy proofs. A latex condom which has adequate instructions and sufficient material strength to block other infections is likely to be allowed to add AIDS to its disease-prevention claims with a minimal amount of FDA review. The most difficult products may be the clinical laboratory testing equipment whose false positive results on HIV status would carry severe anxiety and social stigma, in addition to unnecessary medical treatment.
Dietary insufficiency and loss of appetite may tend to worsen the medical situation of the person who is struggling with the several stages of clinical illness associated with AIDS. The clinical condition of the patient may lessen the patient's willingness or ability to maintain a steady level of adequate nutrition. Loss of adequate nutrition will weaken the patient, further worsening other medical conditions. Therefore, some food products have been used successfully as adjuncts in the treatment of persons who are suffering from acute clinical signs related to HIV infection. These are known as "medical foods" because their labelling and advertising is oriented to special-purpose patients.

The FDA regulates medical food differently than it does normal food products, on the basis of the labelling claims made for a specific disease state or therapy use. It may be, for example, that a person who is suffering the clinical signs of AIDS could be benefited by a diet high in zinc and Vitamin C, and these could be provided by the right balance of vegetables and normal food products. A specific vitamin or benefit claim for a normal food, addressed to persons who are affected by the HIV-infection, could
be treated by the FDA as a "special dietary food" or "medical food" claim. The FDA is much more likely to challenge these traditional products with new AIDS-related benefit claims as being drugs because this enhanced health-related claims.

A food product becomes a drug product when a claim is made for its benefit as a disease-preventive or mitigating factor. If mitigation, or lessening of the AIDS-related conditions is claimed, then the FDA will treat the "food" as a drug and will challenge its sale, unless the manufacturer has properly complied with FDA's guidelines for the labelling of such foods.

FDA's regulatory program for medical claims of foods is in the course of being totally revised. FDA has approached the issue in two ways, (1) with a medical foods approach which is expected to be issued as a proposal in 1989, and (2) a more general "health claims for foods" regulation which has been proposed, has drawn extensive comment and may be made final in 1989.

In the case of a medical food directed to mitigation of AIDS symptoms, the FDA approach makes a great deal of sense, because products having special benefits for AIDS patients should be properly characterized. Excessive claims (usually accompanied by excessive prices) should be discouraged by the FDA regulatory system. It would be unfortunate if the FDA had no authority to prevent false and misleading claims from deceiving persons afflicted with this HIV related infection.

The separate proposal made by the FDA in the health claims regulations for traditional food products, is essentially
one of claims triggering full disclosure. This health claims labelling control regulation will limit excessive product benefit claims for manufactured or processed foods in normal use, with labelling appropriate to such traditional health issues as excessive fat, cholesterol, and other kinds of illness. The health claims regulation becomes a matter of medical foods regulation when the medical foods are aimed at a specific disease or a specific psychological weakness in the body system. "Eat Munchies, Avoid AIDS infection" is a health claim, while "Munchies Sustain the Iron-deficient AIDS Patient" is a medical food claim.

Section 19.2 - Vitamin Legislation

The FDA also has special jurisdiction, under a 1976 law, to regulate drug claims for vitamins. The vitamin regulation which the FDA had pursued during the preceding ten years was supplanted by a specific congressional bill which established the authority of the FDA to regulated specific disease claims, but restricted FDA's general ability to control vitamin content or potency.

In the case of persons who are HIV-infected, the vitamin legislation is important, because it prohibits the FDA from limiting the content of specific vitamin combinations or potencies. It does not, however, restrain the advertising claims that are made for the vitamin pills or liquids. Therefore, FDA would need to challenge the use of a specific disease reference alleging that this reference to HIV benefits made the vitamin pill or liquid into a drug. FDA is discouraged from doing so by the limitation on its
authority which are found in the 1976 legislation. In most cases, persons who are concerned about medical aspects of nutrition will have to choose carefully among the vitamin products being sold, because the extent of regulatory agency supervision of the content of these nonspecific products claims is limited.

In the history of our health-conscious public seeking therapeutic benefits from vitamins or other health related foods, there has been a long history of consumer fraud, overcharging and failed experiments. The current shortage of FDA enforcement staff and resources means that these claims for vitamin products probably will not be halted by FDA enforcement actions. Therefore, it is an issue for state Attorneys General, the Federal Trade Commission or private self-regulatory bodies to control the vitamin advertising which is aired in the typical consumer marketplace.

When vitamins are sold specifically for mitigation of problems associated with the HIV-infected person's medical condition, the FDA and other agencies should be stimulated to bring enforcement action against false and misleading claims which exaggerate the benefits of a particular vitamin programs for the HIV-infected patients.

Section 19.3 - Food Additive Petitions

It is possible that science may find that the progression of the HIV retrovirus can be affected by the ingestion in the body of certain nutrients, and that these nutrients can be beneficial to the avoidance of the progression of the disease into actual
clinical AIDS. The creation of such a food product would be of significant benefit to persons who are HIV-infected, if science were able to prove the safety and functional benefits of such a material. FDA has control, under the Food Additives Amendments of 1958, over the claims that can be made for products which are added to food and which are not natural, traditional food components. The FDA can regulate these new food sources under the Food Additive Amendments, and can treat the food additives status of these products as the close equivalent of new drug or new medical devices regulation products. The Food Additive process requires an application by the sponsoring company, review of the safety and functionality of the food additive, a published regulation by the FDA in the Federal Register, and an opportunity for comments or objections by interested party.

The food additive petition process could result in an FDA determination that the food material can be used for this new kind of specialty food having an HIV-related medical purpose. It is more likely that the manufacturers of the product will treat it as a drug, and seek FDA approval, since the products of current interest in the AIDS research pipeline are not those regularly ingested as foods, but materials which have vaccine or pharmaceutical benefits for HIV-infected individual. If there should be a food additive approach to mitigating the effects of HIV-infected conditions in the future, this food additive petition process managed by FDA's Center for Food Safety and Applied Nutrition, will become important in the regulatory clearance
Indeed, drug approval allows some risks if they are offset by clear benefits. A food additive faces a tougher approval process because, unlike the case of drug approvals, only the food additive's risks and not its benefits are evaluated by FDA.

Until a specific approval occurs, physicians and researchers working in the AIDS area are probably going to recommend certain traditional foods as a supplement to the dietary practices of persons evidencing clinical signs of AIDS. But the reputable manufacturers probably will not be selling foods which claim to have additives specially intended for relief from the HIV infection, until and unless FDA blesses one of these food substances. There is always the opportunity for false, misleading, and fraudulent claims to be made for readily available food substances, but these, like all other enforcement situations, reflect the problems of inadequate enforcement resources rather than the straight-forward regulatory and product approval functions of the Food and Drug Administration.

An important new policy announcement in 1989 permits individuals to carry into the U.S. a limited personal supply of unapproved drugs; but this supply may be for no more than three months of treatment. All other legal restrictions on smuggling and on quantities of unapproved drugs are still enforced.

An individual U.S. citizen might choose to go to Mexico for treatment with an experimental pharmaceutical available over the counter or by prescription in Mexico. That journey is not in
CHAPTER 20

IMPORTS OF REGULATED PRODUCTS

Section 20.1 - FDA and the Foreign Drug Products

Many people familiar with the HIV infection epidemic are very concerned about the inability of patients to bring in potentially useful pharmaceutical from other countries, such as Mexico, in which experimental therapies are much more rapidly available for patient use. The FDA monitors the borders, through the cooperation of the U.S. Customs Service, and routinely detains and reexports products which do not meet the FDA requirements for new drug approval. In the case of individual smuggling of pharmaceutical products, the penalty for importation of an illegal drug substance may be as severe in the criminal sense as penalties are for importation of controlled narcotic drug products.

An important FDA policy announcement in 1988 permits individuals to carry into the U.S. a limited personal supply of unapproved drugs, but this supply may be for no more than three months of treatment. All other legal restrictions on smuggling and on quantities of importable drugs are still enforced.

An individual U.S. citizen might chose to go to Mexico for treatment with an experimental pharmaceutical available over the counter or by prescription in Mexico. That journey is not in
violation of U.S. Law. The importation by the individual of the drugs available in Mexico for sale here is a violation of U.S. law, and the person could be prosecuted as a drug smuggler if detected at or beyond the border. FDA spends a considerable amount of time on the Mexican border responding to the Customs Service when Customs agents detect a situation involving the possibility of smuggling of a pharmaceutical product. However, even under the 1988 "three month personal quantity" policy change, import of a quantity larger than this short-term personal need amount is still a violation of law.

FDA sampled only 20,000 of the total 1,600,000 imported shipments of FDA-regulated products in 1987, primarily due to limited enforcement resources. But FDA and Customs together react rapidly when there are indications that significant quantities of therapeutic supplies of an unapproved new drug are being imported, especially for sale in the United States.

Section 20.2 - The Drug Importation Process

Legislation adopted by Congress prohibits the reimportation into the United States of prescription drugs which have been exported. The FDA knows that if a prescription drug product is coming into the United States, the shipment will be detained and checked if the incoming product does not already have an FDA approved new drug application. There is a potential criminal violation, or at minimum an FDA seizure of the product, if the import is not under an NDA or IND.
Statistics suggest that the importing of small quantities of a new drug might not be detected. FDA enforcement resource problems and similar limitations for the Customs Service make it likely that a certain number of persons will cross the border with quantities of other nations' approved drugs which are not available for sale in the United States. On a sustained basis, however, the importer faces a high probability that the FDA will detect and challenge importation of such products. The manufacturers overseas are not likely to make commercial-size shipments of drugs intended for use in AIDS patients, because these larger shipments are much more likely to be detected by the FDA and are more likely to be seized or made the subject of a strong enforcement proceeding against the offending shipper.

In order to legally bring a new drug into the United States, the importer of record, usually a pharmaceutical distributor must obtain a new drug application approval or a IND permitting the U.S. use of that new pharmaceutical drug. The product cannot be brought into the United States through Customs unless the FDA paper work has been taken care of in advance. In the typical case, when Customs inspectors receive the paper work from the transportation carrier, they will check to see that the drugs are coming from or to a normal, known source. If the source is unknown, FDA will be notified and Customs will place a hold on the shipment. The FDA then issues a Notice of Detention and Hearing which places the goods "on hold" under the custody of FDA. The notice requires the potential importer to await an FDA hearing
before the goods can be released into the port of entry. If the person importing the drugs does not appear and defend the drugs with a showing of an approved IND or NDA, then the FDA will destroy the drugs and will charge the shipper or the transportation company with all costs of supervision and destruction.

Importers are also responsible for paying customs duties. Depending upon American import barriers in this time of rising protectionist sentiments, these duties could become significant cost barriers against drugs manufactured overseas. As a result, prices of imported drugs to the AIDS patient will reflect these customs duties.

Section 20.3 - Pre-Importation Treatment of AIDS-Related Drugs Prior to NDA Approval

Foreign sources of pharmaceutical drugs for IND use are entirely legitimate. The FDA does not make a distinction between the foreign manufacturer of a drug and the U.S. manufacturer, so long as the foreign manufacturer is registered and meets all of the FDA requirements for importation.

The FDA requirements for importation typically begin with the IND. If the manufacturer wishes to file for an IND, it must have a defined protocol, a U.S. investigation site, a U.S. clinical investigator, a drug registration number for the foreign manufacturer of the drug, and it must wait the 30 days after filing the complete IND. If a clinical hold is placed on the research,
then the IND is not considered active and the drug may not be imported to service that IND experiment.

The IND hurdles are likely to be eased for manufacturers of high-visibility drugs such as those for AIDS. The FDA will generally work cooperatively with a drug submitter from another country who wishes to conduct U.S. clinical studies on a high-interest, high-profile drug for the treatment of AIDS patients. The manufacturer in the other nation typically hires a U.S. consulting firm which is familiar with the IND process, and that consulting firm representing its overseas company provides the preclinical documentation, translations, clinical placement work, technical writing, and follow-through needed for successful completion of the IND study.

Importation of an IND drug is not difficult once the IND paperwork is in order. Caution statements will be required on the containers. Importation of a drug for which an approved NDA exists may be somewhat more difficult. The product which is the subject of the approved NDA should be labelled identically and manufactured identically with the U.S. version of the same drug. This means that unique U.S. labels will be affixed before the drugs come into the U.S. market. In this case, if a U.S. pharmaceutical firm had an approved NDA for foreign-manufactured drugs to be used for the treatment of a kind of pneumonia associated with HIV-infected persons, then the same kind of drug manufactured by a foreign licensee of the U.S. manufacturer should also be acceptable for importation. The FDA may take some time to unravel the complicated

293
paperwork of approval and licensing, but the drugs will not face a significant barrier of entry at the border.
CHAPTER 21

The Physician and the Food and Drug Administration

Section 21.1 - Prescribing of Drugs for Unapproved Uses

Doctors have much more "freedom of choice" in AIDS-related therapies than do patients. Federal law allows a physician to determine what uses are acceptable to that physician for that patient with that pharmaceutical. Individual physicians can prescribe an individual drug to an individual patient for a use which is not described in the drugs' label without violating the law. This policy preserves the flexibility of the individual physician to make the determination that the product might be useful for the HIV-infected person. The physician for the HIV-infected person is free to try all kinds of medications in order to see which ones are most beneficial to the patient. This prescribing is not a violation of the Food, Drug, and Cosmetic Act.

It would be a violation, however, if unapproved uses were routinely promoted by the manufacturers or sponsors of the drug, who bring the suggestion to the physician that the drug be used for that new purpose. FDA is very unwilling to permit sponsors or manufacturers to stimulate individual physicians toward the use of approved drugs for unapproved purposes. FDA recognizes that the Act does not prohibit the doctor's prescribing of a cancer drug or
a tuberculosis drug for an HIV-infected patient, but the sponsor of the cancer or tuberculosis drug must obtain supplemental NDA clearance before that sponsor makes any representations to physicians about the AIDS-related uses.

In stating that the physician is protected from Food, Drug and Cosmetic Act liability, it is not to be inferred that the patient is not protected. Medical and pharmacy licensing boards of the state, as well as state laws relating to inappropriate use of drugs, coupled with normal products liability concerns, cumulatively serve to restrain the physician from inappropriate use of a pharmaceutical. If the pharmaceutical were used for an inappropriate purpose, the physician making that determination concerning the use of the drug would be exposing himself or herself to very large potential liabilities. On the other hand, because the manufacturer would not be involved in the professional decision of the individual physician to prescribe and administer the drug, FDA would not present a potential source of liability for manufacturers, notwithstanding the prescribing habits of individual physicians.

In the 1985 U.S. Supreme Court case of Heckler v. Chaney, the issue of unapproved use of drugs became a major Supreme Court precedent. The Supreme Court refused to order the Food and Drug Administration to stop a state prison medical ward from administering a lethal injection of a new drug into the veins of a convicted killer who was on death row. The drug was not labeled for use in human executions, of course. The state viewed this
manner of execution of prisoners as more humane than its historical use of hanging. The FDA decided that the agency's regulatory power would not be used to control the unapproved dispensing of the particular injectable drug product, even though the dispensing for purposes of fatal execution was not on the product's approved label. It would be an absurd exercise for the FDA to receive, process, and examine clinical studies of human executions with particular drugs, in order to allow a label claim that the particular product could be used to kill human beings.

The U.S. Supreme Court upheld the right of the FDA to determine its own jurisdiction concerning unapproved uses of new drugs. FDA was told by the Supreme Court that it could select its choices for enforcement targets in a way which served its own overall priorities. The FDA cannot be compelled by the courts to begin enforcement cases against a particular target. The broad discretion which the FDA has to challenge the unapproved uses of a drug will not be altered by judicial decrees. The U.S. Supreme Court in the Chaney case would not order the FDA to bring an enforcement action against the prison authorities. Similarly, it can be presumed that as long as the individual physician does not enter into a more formal distribution system with the help of the sponsor or manufacturer of the drug, the FDA probably will take no action against the individual physician's decision to prescribe the drug for a particular purpose.
Section 21.2 - Malpractice and Liability Issues

The physician presented with the AIDS patient who shows clinical signs of disease is quite properly frustrated that the pace of drug approvals has not produced a series of effective drug products which may be prescribed for the benefit of such a patient. Instead, the physician must consider a variety of other medications which could be used in conjunction with some form of therapy to attack the malady. The physician may choose to use a range of products which have no label statements for uses related to AIDS.

The physician takes on additional malpractice liability when he or she uses a drug for a condition such as an AIDS-related symptom for which there are no approved products. The choice being made here is for the benefit of the patient, but the choice is being made in a way which leaves the individual physician without any ability to pass on liability for adverse drug effects to the drug's manufacturer. The drug manufacturer, while remaining liable for negligent manufacture or for certain forms of defectiveness in the intended uses of this drug, is probably not going to have civil liability to patients whose profile did not fit that of the approved labelling. For example, the manufacturer of a drug will probably not have to pay damages to a person who is injured by the drug in the course of experimental use in a therapy which the manufacturer did not recognize, recommend or sanction through its label.

The manufacturer's decision to claim that its drug works for one indication and not another is probably the result of a
decision that the product could not easily be tested for that additional indication. The FDA accepts the decision of the manufacturer not to apply for new drug applications for the additional medical indications. Picking the indication to be tested involves research costs, sales, and profit projections. That is an entirely free choice by the manufacturer. If a serious injury occurs from a nonapproved use of the drug, and the manufacturer is not responsible for the unapproved use, then the malpractice and products liability concerns for the individual physician remain very high. Malpractice principles of liability will vary from state to state. Physician liability for prescribing a drug for an unapproved use is a matter of state law, so this book will not attempt to resolve the issue of liability for an AIDS drug effort which fails or causes injury. Legal counsel familiar with the malpractice laws in a particular state should be able to provide guidance on this complicated and timely issue.

Section 21.3 - Physician Investigation of Drugs

FDA rules allow individual physicians to become independent sponsors of investigational new drug ("IND") applications. The FDA expects clinical safeguards to be maintained, but will not demand the same volume of paperwork from an individual doctor as would be expected from a drug manufacturer. Results of the IND work will be part of individual medical publications but usually will not lead to FDA approval of a major new chemical or therapeutic agent. Rather, the investigation will
stimulate larger-scale test work or will disprove a theory of alternative therapy. FDA could also make a cash grant to the physician investigator for an "orphan drug" investigation.
CHAPTER 22

Advertising and AIDS

Section 22.1 - AIDS Advertising and the FDA

True consumer protection must include oversight, not only of the product itself, but also of what is stated or claimed about it in advertising and sales campaigns. Advertising includes all of the promotional material which is distributed for a drug, but which does not physically accompany the drug product to the retail store or other point of sale. An advertisement appears in a medical journal or (for nonprescription drugs) on television or on radio, or on billboards. The actual product package, the flyers in stores, or the free books given away with each bottle of the magical cure material are considered "labelling" of the products to which they relate, and such claims are fully subject to FDA jurisdiction.

The manufacturer of a product which is approved through the NDA or the PMAA process by the FDA will have to keep its advertising within the balance of the acceptable claims which the FDA has approved on labelling. The FDA can take regulatory actions against unapproved advertising claims which go well beyond the claims permitted on the product's labelling.
Typically, manufacturers of legitimate AIDS-related products will be cautious in the drafting the product claims so as to stay as close as possible to categories in the FDA approved labelling. If the FDA wishes to attack an advertisement, it must first establish whether or not the product is a prescription drug or a prescription medical device, because if the product is not a prescription product, the FDA would not have jurisdiction over its advertising. The FDA may determine that the advertisement accompanied samples of the drug, and thus was "labelling". In such a case, the FDA would have jurisdiction over its dissemination even though the product was for over-the-counter use rather than a prescription drug or medical device.

After this analysis, then the FDA will examine whether the advertisement was misleading, especially where its stated claims omitted some material facts about which the purchaser should have been told. This misleading nature of the advertising claim would be subject to FDA's jurisdiction if the product were a prescription product. FDA could charge that the advertisement was going beyond or creating an inference greater than the effectiveness claim which the FDA permitted in the initial labelling. The manufacturer is free to offer a supplemental NDA which FDA could review and approve, which would make the additional benefit claims in the course of labelling, and therefore make such claims legitimate for advertising as well. But it is more likely that the FDA will not have reviewed the particular advertising, and it becomes a matter of judgment for the FDA as to whether to attack
the legality of the product's advertisement. This judgment over
advertising is best applied by the FDA after thorough examination
of what is being done in the market place by other companies.

If the FDA drug advertising group believes that it needs
an enforcement action against one company to deter others from
inappropriate conduct, then the advertising may be challenged in
court by a product seizure action. In most cases, the FDA uses
informal means of communication and persuasion to suggest to the
manufacturer that it may wish to limit the offending type of claim
in the future.

Section 22.2 - Advertising and the Federal Trade Commission

In the case of over-the-counter drugs or medical devices,
any AIDS-related advertising claims will probably be false. FDA
has for years observed false claims being made about common well-
established products. These products do not generally have
efficacy against HIV-infection to the extent that such efficacy be
established by adequate and well-controlled studies. Therefore,
the FDA could ordinarily presume that if it saw an over-the-counter
drug being sold with an AIDS claim, that the claim is misleading
(a "misbranded" drug claim), or the claim is a violation of the
FDA's requirement for prior approval of the new indication for such
a product before it is marketed (an unapproved new drug claim).

The Federal Trade Commission, an independent federal
regulatory agency composed of five commissioners and a large
advertising review staff, responds to complaints concerning
misleading advertising. The FDA and FTC work closely together against fraudulent or false advertising claims for drug products. FDA takes the prescription drug categories, and the FTC takes the over the counter drug and medical device categories. The FTC challenges typically result in a consent order which settles the charges and promises that the manufacturer will not be involved in that kind of claim in the future.

Under FTC precedents, the manufacturer must have adequate clinical substantiation before making any representation of health-related benefits for a product. This health-related benefit claims policy generally resembles the goals of the FDA's new drug application policy, though the FTC is focused exclusively on what is being told to consumers about the benefits of the product. The FTC is not generally concerned with claims made directly to physicians, microbiology laboratories or other experts. Rather, the FTC focuses upon protecting the less sophisticated public while the FDA regulates misleading statements made to the higher educated group of sophisticated clinicians.

Section 22.3 - Other Advertising Controls

The advertising claims to be made for a product intended for AIDS or HIV-infected persons are also controlled by the state Attorneys General, who have taken an active role in policing false advertising throughout the United States. The FDA and FTC cannot reach all of the cases of inaccurate or misleading claims for products, and these state enforcement agencies have an important
role in selecting and policing challenges to inappropriate drug product benefit claims. Advertising control by a state is generally done in the form of prosecutions, seeking misdemeanor convictions or civil penalties for false and misleading claims resulting from a consumer fraud within the state. For example, a body of HIV-infected persons might be willing to try any new therapy offered by a start-up medical institution. If the institution did not have a factual scientific basis for its claims of benefits from this new therapy, then the state Attorney General might become involved in an enforcement case in which the product's and institution's integrity would be tested through the hearing process of the state courts.

There may also be fraud charges brought under federal mail fraud statutes by postal inspectors against AIDS remedies sold by mail. Or the FDA and FTC might suggest to the complainant that the offending advertisement should be tested in the voluntary advertising self-regulatory program of the Council of Better Business Bureaus, National Advertising Review Board Division. If the advertiser is reputable, it will usually participate. These kinds of voluntary and non-federal dispositions of advertising disputes have become more frequent and more frequently observed since the relatively weakening of the Federal Trade Commission's advertising control activities in the 1980s.

Cleaning and disinfecting products which make anti-AIDS claims fall under the regulatory authority of the U.S. Environmental Protection Agency ("EPA"). The makers of one
chemical were fined $10,000 for AIDS-related labeling materials which did not have EPA approval. The simplest way to judge whether an advertised disinfection claim is truthful is to look on the product label for "EPA Reg. No. ____," which signifies that EPA reviewed the actual tests of the product against live HIV-virus particles.
CHAPTER 23

CONCLUSIONS

The epidemic of HIV retrovirus forces us to confront every systemic problem in our country's regulation of health related products. Everything from advertising to zoology is involved in the struggle, from the selection of the appropriate animal model for vaccine trials to the end of the pipeline when we will respectfully disagree with one another about the claims which can be advertised about therapeutic benefit. The selection of the appropriate vehicle, and the selection of the appropriate drug or biological entity to be pursued has extremely important consequences for regulation of the developer. This book has shown some of the complexities of AIDS drug development.

As this book has related, the Food and Drug Administration is an important societal asset. FDA's function as the bottleneck of drug approval has been criticized. But that bottleneck has the ability to produce a level playing field among competing companies, as well as to produce a quality drug product upon which the public can usually rely with great assurance. Manufacturer of products subject to FDA jurisdiction generally get fair treatment, although it is not always expedited.
In the case of AIDS products, approval mechanisms are as expedited as one can expect and as fair as one can expect. What typically holds up a drug is miscommunication, inability of regulator and the regulated parties to understand one another's needs, and higher priorities of items which are already on the agenda of the FDA.

California's independent approach is novel and it promises to produce good results. Further conclusions can be drawn about the adequacy of the California System after it has been in operation for several years. California's system is a laboratory, stimulating research. It is too early to tell whether individual state solutions to the symptoms presented by this dreaded epidemic will be effective to the extent that they should be emulated in other states as well.

Increased national prioritization of AIDS vaccine and drug research will be necessary as the means to fill the drug pipeline. Streamlined drug regulation methods exist, which make for a more rapid progression from "good science" to "good products". There is still room for improvement, but filling the pipeline with beneficial candidates for approval is a vital prerequisite to FDA approvals.
The epidemic of HIV retrovirus forces us to confront every systemic problem in our country's regulation of health related products. Everything from advertising to zoology is involved in the struggle, from the selection of the appropriate animal model for vaccine trials to the end of the pipeline when we will respectfully disagree with one another about the claims which can be advertised about therapeutic benefit. The selection of the appropriate vehicle, and the selection of the appropriate drug or biological entity to be pursued has extremely important consequences for regulation of the developer. This book has shown some of the complexities of AIDS drug development.

As this book has related, the Food and Drug Administration is an important societal asset. FDA's function as the bottleneck of drug approval has been criticized. But that bottleneck has the ability to produce a level playing field among competing companies, as well as to produce a quality drug product upon which the public can usually rely with great assurance. Manufacturer of products subject to FDA jurisdiction generally get fair treatment, although it is not always expedited.
In the case of AIDS products, approval mechanisms are as expedited as one can expect and as fair as one can expect. What typically holds up a drug is miscommunication, inability of regulator and the regulated parties to understand one another's needs, and higher priorities of items which are already on the agenda of the FDA.

California's independent approach is novel and it promises to produce good results. Further conclusions can be drawn about the adequacy of the California System after it has been in operation for several years. California's system is a laboratory, stimulating research. It is too early to tell whether individual state solutions to the symptoms presented by this dreaded epidemic will be effective to the extent that they should be emulated in other states as well.

Increased national prioritization of AIDS vaccine and drug research will be necessary as the means to fill the drug pipeline. Streamlined drug regulation methods exist, which make for a more rapid progression from "good science" to "good products". There is still room for improvement, but filling the pipeline with beneficial candidates for approval is a vital prerequisite to FDA approvals.
CHAPTER 23

CONCLUSIONS

The epidemic of HIV retrovirus forces us to confront every systemic problem in our country's regulation of health related products. Everything from advertising to zoology is involved in the struggle, from the selection of the appropriate animal model for vaccine trials to the end of the pipeline when we will respectfully disagree with one another about the claims which can be advertised about therapeutic benefit. The selection of the appropriate vehicle, and the selection of the appropriate drug or biological entity to be pursued has extremely important consequences for regulation of the developer. This book has shown some of the complexities of AIDS drug development.

As this book has related, the Food and Drug Administration is an important societal asset. FDA's function as the bottleneck of drug approval has been criticized. But that bottleneck has the ability to produce a level playing field among competing companies, as well as to produce a quality drug product upon which the public can usually rely with great assurance. Manufacturer of products subject to FDA jurisdiction generally get fair treatment, although it is not always expedited.
In the case of AIDS products, approval mechanisms are as expedited as one can expect and as fair as one can expect. What typically holds up a drug is miscommunication, inability of regulator and the regulated parties to understand one another's needs, and higher priorities of items which are already on the agenda of the FDA.

California's independent approach is novel and it promises to produce good results. Further conclusions can be drawn about the adequacy of the California System after it has been in operation for several years. California's system is a laboratory, stimulating research. It is too early to tell whether individual state solutions to the symptoms presented by this dreaded epidemic will be effective to the extent that they should be emulated in other states as well.

Increased national prioritization of AIDS vaccine and drug research will be necessary as the means to fill the drug pipeline. Streamlined drug regulation methods exist, which make for a more rapid progression from "good science" to "good products". There is still room for improvement, but filling the pipeline with beneficial candidates for approval is a vital prerequisite to FDA approvals.