Burroughs Wellcome and AZT (A)

Extreme diseases demand extreme cures.

—Hippocrates.

On the morning of Thursday, September 14, 1989, seven men from the activist group ACT UP (The AIDS Coalition to Unleash Power) entered the New York Stock Exchange dressed in business suits and wearing forged name tags of the investment bank Bear Stearns. A minute before trading was to start, five of the men chained themselves to the railings of the balcony above the trading floor, activated an electronic foghorn smuggled into the building, and unfurled a large banner that read: "Sell Wellcome." The other two men photographed the protest action, including the ensuing pandemonium on the trading floor, and immediately rushed the images to the international media. Although police quickly removed the intruders from the NYSE, hundreds of protesters marched in sympathy on the streets outside the building. Concerted demonstrations were held that day as well in San Francisco and London.¹

Wellcome PLC, the target of the protests, was the British pharmaceutical company whose American subsidiary, Burroughs Wellcome Co., had brought to market the only drug approved in the United States for use in the treatment of AIDS (Acquired Immune Deficiency Syndrome). ACT UP and other advocacy groups for people with AIDS decried the continuing high price of the drug, AZT, which retailed for approximately $8000 per person per year at the time. "Wellcome is involved with shameless profiteering," declared a hospital administrator in a front page article appearing in the Wall Street Journal the day after the protest. Executives at Burroughs Wellcome's North Carolina headquarters disagreed fundamentally with the assertions of its critics. "There's a myth out there that we're robber barons, ripping people off," contended David Barry, MD, the firm's vice president of research. "It would be theoretically possible for us to give away all our drug. Everyone would get it for a while, and then we'd go bankrupt."² Nevertheless, Barry and other Burroughs Wellcome executives were perplexed about the demonstrations and wondered what response would be most appropriate.

¹ Bruce Nussbaum's Good Intentions (New York: Atlantic Monthly Press, 1990) served as a particularly useful reference for this and other sections of the case.
Wellcome PLC

Wellcome PLC (public limited corporation) was one of the world’s oldest multinational pharmaceutical firms. The firm was founded in 1880 by two American druggists in London, Silas Burroughs and Henry Wellcome, and over the decades its scientists had won half of the eight Nobel prizes for medicine awarded to industry. From 1936 to 1985, the company was registered as a charitable trust, using the income distributed by the business to promote research in medical and allied sciences. In 1986, 25% of the company’s shares were floated on the London International Stock Exchange, while the remaining shares were retained by The Wellcome Trust, Britain’s largest charitable organization. By 1989, Wellcome’s annual revenues reached £1.4 billion, almost half of which originated from its American Burroughs Wellcome subsidiary (see Exhibit 1 for data on Wellcome’s financial performance). The company employed almost 18,000 people worldwide, 19% of whom were engaged in research and development. Wellcome’s best-selling drugs included medications for herpes (Zovirax), AIDS (Retrovir4), and allergies/colds (Actifed and Sudafed). Exhibit 2 presents data on Wellcome’s revenue by product group.

From its earliest years, Wellcome was regarded as an innovator, pioneering the tablet as an alternative to medical powders and establishing the practice of direct sales calls to physicians (“detailing”). The firm’s early emphasis on research, particularly charitable research, led it to emphasize less profitable areas such as tropical or obscure diseases. Wellcome’s research on antiviral drugs, dating back to the 1940s, was one of the first and most extensive efforts in the industry. By the mid-1980s, the firm had the fourth largest drug research staff in the world, despite ranking 24th in prescription drug sales. Because of the firm’s strong research orientation, it was sometimes referred to by its employees and outside analysts as “Wellcome University,” highlighting both its academic prestige as well as its historic emphasis on science over profits.

Acquired Immune Deficiency Syndrome (AIDS)

Mysterious Appearance of AIDS

In the late 1970s, the medical community began to take notice of an unusual rise in the incidence of several rare diseases, including Pneumocystis carinii, an uncommon form of pneumonia, and Kaposi’s sarcoma, a rare form of skin cancer characterized by bruise-like purple spots on the body. By themselves, these illnesses were not incurable. However, those afflicted suffered from unexplainable immune deficiencies that, in combination with these diseases, appeared to always lead to death. Many of the victims also experienced depression, severe weight loss, and memory loss similar to that of senility before succumbing to the disease.

At this time the patients were almost always urban males from San Francisco, Los Angeles, or New York. A distinguishing feature shared by these men was their homosexuality, thus leading some physicians to refer initially to the condition as Gay-Related Immune Deficiency Syndrome (GRIDS). By 1982, after it was apparent that certain members of other groups, including drug addicts and hemophiliacs, were also suffering from the condition, the medical community settled upon the more neutral descriptor: “Acquired Immune Deficiency Syndrome” (AIDS). In April 1983, the Center for Disease Control in Atlanta reported roughly 3,000 cases of AIDS, including 1000 fatalities (see

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3 Based on an average exchange rate of $1.68=£1 for 1989, revenues were approximately equal to $2.37 billion.
4 Retrovir was Wellcome’s trademarked brand name for zidovudine, which was itself the generic name of the chemical compound azidothymidine (AZT).
Appendix 1 for an overview of key U.S. government agencies involved with AIDS, and Exhibit 3 for data on reported cases of AIDS and deaths attributed to AIDS in the 1980s).

In spite of the growing number of deaths from AIDS, little attention was devoted to the syndrome in the popular press until reports emerged of heterosexuals contracting AIDS via blood transfusions. Even so, the general public remained largely unaware of AIDS or simply regarded it as an affliction of certain marginal groups in society. Some religious fundamentalists interpreted AIDS as a plague sent by God to punish homosexuals. Although the National Institutes of Health devoted some research funds to studying AIDS, its spending levels appeared low in comparison with funding for such illnesses as Toxic Shock Syndrome and Legionnaires’ Disease. One person with AIDS (PWA) commented about the limited governmental response: "I wonder if it had been 1,500 Boy Scouts, what they would have done."6

**Discovery of the Human Immunodeficiency Virus (HIV)**

By 1983, scientists had concluded that AIDS was linked to some blood-borne agent, although the precise cause of the syndrome was still unknown. A year later, scientists in France, followed shortly thereafter by researchers at the U.S. National Cancer Institute, linked AIDS to a virus that was eventually termed the Human Immunodeficiency Virus or HIV. Researchers believed that after HIV entered a person’s bloodstream, it gradually destroyed a key part of the body’s immune system (white blood cells), leaving the affected individual vulnerable to a variety of infections and diseases, including the Pneumocystis carinii pneumonia (PCP) and Kaposi’s sarcoma observed in many AIDS patients. However, the time elapsed between infection with HIV and the onset of AIDS itself (i.e., the emergence of so-called “opportunistic” infections) could differ widely from person to person. In fact, a person harboring HIV could be ignorant of the fact for months or years yet spread the virus to others.

In spite of its devastating potential, scientists established over time that HIV was an extremely fragile virus that could not be spread through casual contact in the manner of such viruses as the common cold. Instead, HIV could be passed only through direct contact between a body fluid of one person and that of another. Even when such direct exposure to HIV took place, the virus would not necessarily take hold in the body of the previously uninfected person. However, at that time, scientists were at a loss to explain why direct exposure to HIV did not always result in infection or why the speed of progression from HIV to AIDS differed so dramatically from person to person. More disturbingly, medical researchers had little to offer in terms of AIDS treatments, much less a cure or vaccine.

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5 According to a Congressional Research Service report, in 1982 the National Institutes of Health had spent $36,100 per person dead from Toxic Shock Syndrome; $34,841 per person dead from Legionnaires’ Disease; but only $8,991 per AIDS death. Figures cited in Randy Shilts, And the Band Played On (New York: St. Martin’s Press, 1987), pp. 157, 186.

6 Ibid, p. 335.

7 Unprotected anal or vaginal intercourse and the sharing of hypodermic needles appeared to be two particularly risky behaviors in terms of the likelihood of HIV transmission if the virus were present.
Search for AIDS Treatments

Scientific Challenges

When infected with a virus, the human body generally produces proteins known as antibodies that are designed to attack and destroy the invading virus. However, these antibodies are not powerful or plentiful enough to eliminate certain viruses, including HIV. Therefore, scientists attempt to devise alternative means of attacking such viruses, either by creating vaccines that will help the body produce more effective antibodies prior to infection, or by designing drugs that will destroy the virus once it has entered the body. Antiviral treatments are particularly difficult to develop, however, because viruses, like guerilla fighters, can often hide very effectively in the complex landscape of the body. In contrast to other infectious organisms, viruses can multiply only inside living cells. Thus, any drug designed to destroy the virus might instead do more damage to the body’s healthy cells while the virus continues to spread. HIV was an unusual type of virus, a so-called retrovirus,\(^8\) that had previously been found to exist only in animals. Furthermore, HIV appeared to mutate, creating variations of the virus in addition to lying dormant for years like a Trojan horse inside the body.

Because of the complete absence of any drugs approved for use against HIV, people with AIDS in the early 1980s searched desperately for any compound that could conceivably halt, if not reverse, the deterioration of their immune systems or that could help the body recover from the various opportunistic diseases associated with AIDS. In some cases, PWAs traveled to Mexico, where local pharmacies provided access to various unregulated anticancer and other compounds. In the United States, a network of informal lay researchers, often linked by newsletters, began conducting underground trials of their own on drugs from outside the country or from kitchen laboratories. In general, PWAs were frustrated with the apparent inability of the medical community to find a treatment and with the unwillingness of the U.S. government to sanction the use of experimental medications.

Drug Development Process

By the 1980s, most new drugs were discovered through an expensive trial and error process comparable conceptually to oil exploration, where typically many "dry holes" were drilled before any petroleum was actually located. This type of effort required massive allocations of time and financial resources to cover the costs of pursuing false leads and for taking promising new compounds through the regulatory approval process (see Appendix 2 for an overview of the discovery and approval process for new drugs). In the United States, the federal government sometimes participated as well in the development process, either indirectly, through funding basic research at university laboratories and at the National Institutes of Health or, more directly, in cases requiring urgent attention, through collaborations with pharmaceutical firms.

For pharmaceutical companies, a primary incentive for developing new drugs was the prospect of obtaining patent protection and hence, exclusive rights to their discoveries over a 17-year period. Patent rights were particularly valuable in the U.S. market, where firms were typically allowed to set product prices themselves, as opposed to through negotiations with the government, as was common abroad.\(^9\) The Orphan Drug Act of 1983 provided additional incentives in the United

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\(^8\) Retroviruses are composed of the genetic material RNA. In the early 1980s, scientists had only limited research experience with retroviruses, which transcribe (transform) their RNA into DNA before attacking the body’s cells.

\(^9\) In some cases, these “negotiations” represented little more than a perfunctory approval by the appropriate government agency of the manufacturer’s proposed price. At other times, the negotiations were more contentious.
States for the development of new drugs for rare diseases by awarding tax incentives, grants, and guaranteed seven year marketing exclusivity\textsuperscript{10} to firms for products applicable to patient groups numbering up to 200,000. Besides financial incentives, pharmaceutical firms and individual scientists could anticipate international recognition and prestige for major life-saving or life-improving discoveries.

Despite these broad incentives, pharmaceutical companies in the mid-1980s were somewhat skeptical about pouring significant sums of money into the development of drugs for the AIDS market. Prior experience with retroviruses was limited and the prospect of working with the deadly AIDS virus, even in a laboratory setting, was viewed as dangerous. In addition, the market for AIDS drugs appeared very small at that time compared with markets for the treatment of cancer or diseases affecting the cardiovascular or central nervous system. Nevertheless, one major pharmaceutical firm, Wellcome, was anxious to bring its historic expertise in antiviral research to bear on finding a treatment, if not a cure, for AIDS.

### Burroughs Wellcome and Compound S

In the mid-1970s Wellcome’s American subsidiary, Burroughs Wellcome, was heavily involved in antiviral research that ultimately led to the commercialization of the anti-herpes drugs trifluridine (trademarked "Viroptic") and acyclovir (trademarked "Zovirax"). At that time, the subsidiary began studying retroviruses as well, although it was then unclear what role these viruses played in human diseases. In 1977, Burroughs Wellcome augmented its viral research capabilities through the hiring of Dr. David Barry, a physician employed at the FDA’s Division of Virology, who was particularly well-versed in both clinical and regulatory matters.

In the summer of 1984, Dr. Barry, inspired partly by a visit to Burroughs Wellcome by one of the French co-discoverers of HIV, decided to press ahead with an ambitious new goal: to find an antiviral that would be effective against the AIDS virus. Barry, by that time vice president of research for Burroughs Wellcome, contacted Dr. Dani Bolognesi, a retrovirus expert at Duke University, to assist in the development effort. Bolognesi had previously helped test Wellcome drugs and possessed the laboratory facilities necessary to work with the dangerous AIDS virus.

During the next few months, Burroughs Wellcome scientists began the tedious, time-consuming process of screening compounds for further testing against live HIV. According to Phillip Furman, head of viral research: “We looked at all our known antivirals on the off chance that one would work against retroviruses.”\textsuperscript{11} There were plenty of compounds to choose from, given that the company routinely created over 1,500 novel compounds a year. However, Barry decided to restrict the search to those drugs that had already undergone testing in animals or in humans because these would be quicker to develop for commercialization. Most of the compounds screened were rejected since they either killed too many cells or too few viruses. However, several dozen promising substances were sent both to Bolognesi and to FDA laboratories in late 1984 for testing against HIV.\textsuperscript{12}

Bolognesi informed Barry in the meantime that a close friend, Dr. Samuel Broder of the National Cancer Institute (a branch of the National Institutes of Health), had become chairman of the Public Health Service Committee on AIDS Therapeutics. In this capacity, Broder had begun travelling across the nation, exhorting pharmaceutical companies to conduct more research on HIV.

\textsuperscript{10} This period of exclusivity would be valid even if the substance was not patentable or if its patent had expired.


\textsuperscript{12} Given the relative newness of the testing processes and their unknown degree of accuracy, Barry felt that it was important to have the compounds evaluated at multiple sites.
and AIDS and encouraging these firms to send samples of promising drugs to his lab for testing. In October 1984, at the invitation of Burroughs Wellcome, Broder traveled to the firm’s headquarters in Research Triangle Park, NC to discuss his own efforts in searching for a treatment for AIDS and to offer testing services. Barry subsequently forwarded to Broder many of the compounds that were also under evaluation by Bolognesi and the FDA. In each case, compounds were given code names to preserve Burroughs Wellcome’s proprietary position as well as to preclude testing biases.

On November 28, 1984, Barry sent "Compound S" to the FDA for testing. The chemical compound was, in fact, azidothymidine (AZT), a substance first synthesized by Dr. Jerome Horwitz of the Detroit Institute for Cancer Research in 1964. After the drug proved to be ineffective against cancer at that time, it remained unpatented in the public domain. In 1974, West German scientists discovered that AZT was effective against certain retroviruses in mice. However, this work was virtually ignored because retroviruses had not yet been found to affect humans. In the early 1980s, Burroughs Wellcome chemist Janet Rideout resynthesized and studied the compound as an antibacterial. Although these initial investigations proved fruitless, company scientists determined in 1984 that AZT might be effective at interfering with HIV replication, thereby slowing down, if not arresting, the breakdown of the body’s immune system and the subsequent appearance of AIDS.13

After testing Compound S, the FDA reported that it, like other compounds submitted by Burroughs Wellcome, did not appear to offer promise in the fight against AIDS. Barry, frustrated with the disappointing news, sent Compound S to Bolognesi’s laboratory in December to be tested through an alternative process. Much to Barry’s delight, Bolognesi concluded that the compound appeared to be effective against HIV in the test tube. As a “tiebreaker,” Barry shipped Compound S to Broder’s NIH laboratory in February 1985, indicating that he wished to proceed with human testing if the results were positive. Within two weeks, Broder reported back excitedly that ‘S’ was by far the most effective anti-HIV compound tested by the NIH to date. Soon thereafter, Broder flew down to Burroughs Wellcome headquarters to encourage the firm to initiate the costly clinical trial process that would be required before the drug could even be considered for regulatory approval. Barry had already obtained the necessary commitment from his superiors in the United States and from Wellcome’s top management in London and had begun preparations for the first testing of AZT in humans. Meanwhile, Wellcome filed for a British patent for the use of AZT against the retrovirus HIV.

In order to conduct U.S. clinical trials on AZT, Burroughs Wellcome was required to apply to the FDA for “Investigational New Drug” (IND) status for the drug. In preparing the application, the company compiled archival data from Burroughs Wellcome’s earlier tests with AZT in laboratory animals and more recent data from tests in Broder’s laboratories and its own. Throughout this period, Barry maintained regular contact with Dr. Ellen Cooper, the head of the FDA’s antiviral section, whom he knew from his former years of interaction concerning acyclovir. In June 1985, Cooper granted approval for IND status in a record-breaking five working days after receiving the application. In July, Burroughs Wellcome gained Orphan Drug status for AZT and shortly thereafter, the firm applied for a U.S. patent for the drug. Although the patent was originally rejected due to insufficient data, it was subsequently approved when the test data from several laboratories, including Broder’s, was added to the application.

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13 AZT seemed to mimic molecules that HIV required for reproducing itself. By repeatedly “fooling” the virus to attempt replication with AZT molecules, it was hoped that the virus would be prevented from expanding its damaging presence in the body.
AZT Clinical Trials

Safety Trials (Phase I)

Phase I clinical trials typically utilized healthy volunteers to determine the range of tolerable dosages of a drug and any side effects that might occur as a result of taking the drug. However, to accelerate the discovery process of the impact of AZT on AIDS sufferers, the FDA permitted Burroughs Wellcome to conduct its Phase I AZT trials with seriously ill PWA volunteers. These trials were planned at two sites: at the NIH Hospital under Broder’s supervision and at Duke, where Bolognesi and an associate would head up the study team.

On July 3, 1985, Broder and an associate injected AZT for the first time into a human patient, J.R., a furniture salesman from Boston. Initially, J.R.’s temperature rose dangerously; his condition stabilized, however, and the trial continued. After several days, his immune system displayed signs of improvement and his weight showed a moderate increase. Trials were subsequently initiated with twelve more PWAs at the NIH and seven at Duke.

In late July, the American public was shocked at movie star Rock Hudson’s announcement from Paris that he was suffering from AIDS. The fact that Hudson had traveled to France to gain access to an experimental AIDS drug unavailable in the United States was an embarrassment of sorts to the American health establishment. The tremendous publicity surrounding the event, combined with Hudson’s widespread popularity, helped to begin breaking the taboo on mainstream discussion of AIDS and created a new sense of urgency towards finding a treatment or cure for the syndrome. Celebrities such as Elizabeth Taylor lent their support to raise funds for AIDS research, while the U.S. Congress appropriated $234 million to the cause for fiscal year 1986, more than doubling its funding level from the preceding year.

As the Phase I trials of AZT continued in the fall of 1985, Burroughs Wellcome realized that it would soon face a relative shortage of thymidine, a key component in the production of AZT. Broder helped in the short term by tracking down over two hundred pounds of leftover thymidine from within the NIH, which provided it to the company in exchange for an equivalent amount of AZT. In the meantime, Burroughs Wellcome located a small German chemical firm that had produced the substance in the past and negotiated an arrangement to purchase thymidine from the firm by the ton. The trials continued on course through early 1986, with only two of the original volunteers dropping out. Virtually all of the PWAs remaining in the trials gained weight and experienced some improvement in their immune systems, in spite of certain side effects, such as anemia, resulting from the inherent toxicity of the drug.

Efficacy Trials (Phase II)

The apparently strong performance of AZT in the Phase I trials ironically created several dilemmas in the design of the Phase II trials. On the one hand, the standard testing practice of randomly administering the new drug to half of the trial participants, while providing the other half (the control group) with placebos, would deny an apparently beneficial, if not life-saving, drug to every person who fell into the latter group. On a broader level, any PWA denied the opportunity to participate at all in the trials might die before the necessary regulatory approval had been secured for general sale of AZT.

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14 However, the drug, HPA-23, was ultimately shown to be completely ineffective as a treatment for HIV and AIDS.
Scientists traditionally argued that in order to measure accurately the impact of a new drug, it was critical to perform trials on a fairly homogeneous group of patients, all of whom would be given what appeared to be medication, but only half of whom would actually receive the new drug.\textsuperscript{15} By measuring the differences in health indicators of the two groups during the trials, scientists would presumably be able to isolate the effects of the drug itself. An alternative to this "placebo trial" methodology was the use of "historical trials" in which the new drug would be given to all participants in the study. In this case, scientists would compare such indicators as survival rates of trial participants with historical data on persons suffering from the disease. Some researchers, however, argued that historical trials might not yield very useful data in a study of AZT, given changes over time in the speed of diagnosis and improvements in treatments available for various opportunistic infections affecting AIDS patients. Scientists also warned of the impact of the "placebo effect" in historical trials, whereby patients might show temporary improvement due solely to the psychological effect of taking a drug believed to have life-enhancing powers.

The issue of number of participants was a controversial one as well. Phase II trials were typically conducted at a limited number of locations and with no more than a few hundred relatively homogeneous patients in order to keep tight control over the process and to limit the scope of the data-gathering effort. Yet thousands of people were living with AIDS at this time and many thousands more were infected with HIV. For most of these people, AZT appeared to be the only real hope for improvement, at least in the short term.

Burroughs Wellcome eventually decided to employ (double-blind) placebo trials in the Phase II clinical trials of AZT and to restrict participation to about 300 seriously ill PWAs who had suffered a recent episode of the opportunistic disease, PCP. According to Barry, who was responsible for the design of all of Burroughs Wellcome's clinical tests, the choice of placebo over historical trials "was one of the most difficult decisions I ever made."\textsuperscript{16} The company was subsequently criticized for this decision at a congressional hearing conducted by Representative Ted Weiss in July 1986. Nevertheless, Barry was convinced that his decision would result in the most timely and accurate evaluation of AZT.

The Phase II trials began in early February 1986 and were scheduled to continue through December 1986. Although Burroughs Wellcome had hoped to obtain some funding support and participation from the NIH for the trials, the firm ultimately covered all of the Phase II costs itself. Over the course of the trials, a supervisory board of physicians and other clinical trial experts monitored the entire clinical testing process to ensure objectivity. Although many of the participants required blood transfusions as a result of AZT-induced anemia, the trials continued through the summer. In mid-September, the supervisory board asked that the trials be halted, revealing what they felt to be overwhelming evidence in support of AZT's effectiveness: of the 137 participants receiving placebos, 19 had died, whereas only one of the PWAs receiving AZT had died. The statistical significance of the results surprised even Burroughs Wellcome, whose President, Theodore Haigler, remarked: "All of us realized, for the first time, all of a sudden, that we've got a significant product we will have to manage."\textsuperscript{17} Nevertheless, virtually all observers agreed that AZT was not the ultimate treatment for AIDS since the drug merely slowed, but did not reverse, the replication of HIV in the body. In addition, the severe toxicity of the drug remained a continuing concern, particularly in patients with advanced HIV infection.

\textsuperscript{15} These trials were typically conducted in a "double blind" fashion, whereby neither the patient nor the administering physician knew whether the actual drug or a placebo was being taken. Only the independent board of physicians and other experts in clinical trials charged with evaluating the clinical data was informed as to the category to which each participant had been assigned.

\textsuperscript{16} O'Reilly, op. cit., p. 120.

\textsuperscript{17} O'Reilly, op. cit., p. 124.
In January 1987, after an accelerated review of the Phase II trials data, the FDA advisory committee recommended market approval of AZT for use by persons with AIDS;\textsuperscript{18} the FDA consented in March 1987.\textsuperscript{19} This feat of gaining market approval without Phase III trials and within a total time frame of under two years was dubbed by \textit{Fortune} magazine as "the pharmaceutical equivalent of an under-two-minute-mile."\textsuperscript{20} NIH's Broder, who had continued his enthusiastic promotion of AZT throughout the clinical trials process, declared: "I think that this shows what can happen when government and the private sector collaborate."\textsuperscript{21} Shortly thereafter, a second series of clinical trials was initiated to study the effects of AZT on people infected with HIV but not yet showing symptoms of AIDS.

\section*{Bringing AZT to Market}

In moving from the clinical trials to the commercialization phase of AZT, Wellcome faced challenges with respect to both manufacturing and pricing. Over 20 manufacturing steps were required in taking AZT from the raw materials stage to final capsule form. Given the potentially explosive nature of some of the processes as well as the high degree of precision required in various stages of the process, manufacturing facilities would have to be designed carefully. Because of these requirements, Wellcome informed the public that supplies of the drug were likely to be tight in the short-term and that priority would be given initially to persons with the most advanced cases of AIDS. However, since thousands of PWAs were desperately seeking the drug, the capacity for manufacturing AZT on a large scale would need to be developed as soon as possible.

The decision as to how to price AZT also proved challenging. Beyond the costs associated with production, Wellcome felt that it was important to consider the fact that the firm had poured over $700 million into R&D in the early 1980s in its search for new drugs before striking success with AZT.\textsuperscript{22} On the demand side, analysts estimated that the initial market for the drug would be only 15,000 to 20,000 people; future demand was difficult to forecast given uncertainty regarding both the spread the AIDS and the development of alternative treatments. On February 13, 1987, Wellcome announced in a London press release that it would initially set a U.S. wholesale price of $1.88 per 100 mg. capsule of Retrovir, its trademarked version of AZT.\textsuperscript{23} Since patients were to take two capsules every four hours, every day of the year, the annual wholesale price per person for AZT would exceed $8200. With an estimated $0.30 per capsule retail mark-up, the final price to the consumer would exceed $9500 per year, making AZT the most expensive prescription drug on the market. Although Wall Street analysts had projected a relatively high price for the drug, their annual wholesale price estimates had been in the range of $5000-$7000 per year.\textsuperscript{24}

\begin{thebibliography}{9}
\bibitem{18} The advisory committee also recommended and the FDA also approved the use of AZT by persons in an advanced stage of HIV infection referred to at that time as ARC (AIDS Related Complex).
\bibitem{19} During the period October 1986 to March 1987, Burroughs Wellcome provided AZT free of charge to over 4,800 PWAs through a program in which doctors could request the drug for patients with documented cases of PCP. Interview with Dr. David Barry, October 30, 1991.
\bibitem{20} O'Reilly, op. cit., p. 113.
\bibitem{22} Dr. Barry estimated that the firm had spent more than $80 million to develop and test AZT itself. Marilyn Chase, "Wellcome Unit's AZT is Recommended as First Prescription Drug to Treat AIDS," Wall Street Journal, February 17, 1987, p. 11.
\bibitem{23} For the remainder of the case, "AZT" always refers to Wellcome's trademarked drug, Retrovir.
\bibitem{24} Marilyn Chase, "Wellcome Unit's AZT is Recommended as First Prescription Drug to Treat AIDS," Wall Street Journal, February 17, 1987, p. 11.
\end{thebibliography}
The surprise of analysts, however, was overshadowed by the outrage of many PWAs and their advocates. Since most health insurance plans in the United States did not reimburse expenditures on prescription drugs, PWAs would incur sizable out-of-pocket costs to purchase AZT at the same time that many of these individuals faced the loss of employment due to illness or discrimination. Although the most indigent PWAs could rely on Medicaid to pay for AZT, this option would not be available to other AIDS patients unless and until they became sufficiently impoverished. Therefore, PWAs and numerous support groups appealed to Congress for intervention.

Congressional Hearings

In response to charges of price gouging and pleas to Congress for financial assistance for PWAs, the House Subcommittee on Health and the Environment held hearings on "Cost and Availability of AZT" on March 10, 1987. Subcommittee Chairman Representative Waxman, along with several other representatives, questioned Burroughs Wellcome's President Haigler and Vice President of Research Barry extensively during the hearings, excerpts of which appear below.

Rep. Waxman: As I look at the timetable, Burroughs Wellcome has done about a year of screening for drugs and 7 months of clinical trials involving only a few hundred people, as opposed to the thousands that are usually required. You've also received orphan drug status for AZT which should contribute as much as a 72% tax subsidy of your clinical costs. And in addition to that, you get a 25% tax credit for increased research and development. After taxes, how much do you estimate that it cost to get AZT to the point of manufacture?

Mr. Haigler: You have asked a lot of questions there, Mr. Chairman, and I think first, if I might, in arriving at our price for Retrovir, we looked at all of the usual factors that go into—that influence drug-pricing decisions. These certainly include, as you said, the cost of research, . . . the cost of development of the drug, the cost of production of the drug, which includes certainly material costs, which in those cases are a fairly high cost, labor, overhead, yields that come about out of the process itself, waste management, capital expenditure cost, cost of distribution, medical information cost . . . the uncertainties of the market, the uncertainties about the full usefulness of Retrovir, the possible advent of new therapy . . .; all of these factors are usual factors in arriving at a drug-pricing decision. . . . We also, I think, carefully considered two factors that are specific to Retrovir, and that is the high cost of producing this particular drug, and the needs of those patients for whom this drug was developed.

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Rep. Waxman: You did have a quick time frame for getting this drug to [the] FDA, for which you are to be commended. It's essential that we get this drug out there as fast as possible. On the other hand, the shorter period of time and the fewer number of patients involved meant there was less cost to you . . . Do you have a figure that you could give us after you take the tax credits as to how much it cost to do research and development to get to the point of manufacture of the drug? . . .

Dr. Barry: I really honestly don't have that cost figure, because it's difficult to differentiate from our entire research and development program, particularly in the antiviral area. But I did want to

25 Prior to the passage of the Americans with Disabilities Act in 1990, PWAs held no legal protection against discrimination in private sector employment and accommodations.
26 The three excerpts were taken respectively from p. 12, pp. 12-14, and pp. 20-21 of Hearings Before the Subcommittee on Health and the Environment, op. cit.
emphasize that although the number of patients were relatively small compared to the thousands of patients that are often examined in clinical trials, the expense in the relative term was not significantly less from other studies . . .

Rep. Waxman: . . . what you want to do, and you are entitled to, is to recoup your investment. And you say that the pricing structure includes revenues to cover your development costs. If just the 4,500 patients that are now getting AZT continue, your income this year, when you are approved, would be $45 million. By the end of this year, there will probably be 25,000 living AIDS patients in the United States. If all of them take AZT, your income next year would be about $250 million. . . . it looks like you have the potential to recover [your investment, the development cost of this drug] many fold. One pharmaceutical newsletter suggested that your mark-up of AZT is 100%, that half the price is going to be profit. Do you agree with that statement?

Mr. Haigler: I'm sorry, I can't respond to that, Mr. Chairman. I think, to go back to what I said earlier, the potentials of this drug may be there, but it's on the market, what those sales will be, we have no way of really knowing. We certainly don't know what's going to happen in the next year or two as far as new therapies are concerned. Whether this drug will continue to be the drug of choice and really used, we don't know. So I don't think we can speculate on what sales we will have or what profits we might see.

Rep. Wyden: Did you assume that AIDS patients are going to come up with the money? Or did you assume that the government was going to come up with the money?

Mr. Haigler: I guess we assumed that the drug . . . would be paid for in some manner by the patient himself out of his own pocket or by third-party payers. We really didn't get into a lot of calculations along those lines.

Rep. Wyden: I know overseas things are very different. Some [nations] have national systems and can tell a company such as Burroughs Wellcome exactly what they are going to pay. I gather that the United States price doesn't take that into account.

Mr. Haigler: The American pricing structure is a free pricing structure, yes.

After the hearings, Congress appropriated $30 million to subsidize AZT costs for low income PWAs. For its part, Burroughs Wellcome extended free access to AZT for up to three months on a case by case basis in order to give PWAs additional time to secure third-party funding for the drug. Over the next few years, a significant portion of the money spent on purchases of AZT in the United States was to come from government funds in the form of Medicaid and other subsidies.

The Rise of AIDS Activism

Over the course of 1987 and 1988, Wellcome continued to expand its AZT manufacturing capacity, while maintaining a fairly low profile in terms of public relations. However, this period witnessed a surge in visibility on the part of AIDS activists, exemplified most dramatically by the actions of the group ACT UP.
Emergence of ACT UP

In spite of the regulatory approval of AZT, most people with HIV and AIDS remained extremely frustrated in early 1987. Six years and over 20,000 deaths after the first reported case of AIDS, the long-term prognosis for those contracting the disease still appeared bleak. Although AZT offered the hope of slowing the replication of HIV and the onslaught of opportunistic infections, it was not a cure for AIDS, and furthermore, the side effects of its toxicity were worrisome. These facts were particularly troubling since (1) progress on other anti-HIV drugs and treatments for AIDS-related opportunistic diseases was minimal and (2) the prospects for a vaccine seemed remote. Many PWAs and their advocates continued to accuse the Reagan administration of largely ignoring the disease as a result of the association of AIDS with homosexuals and increasingly, drug addicts. In addition, the FDA was accused of relying on cumbersome procedures that delayed or denied PWAs access to compounds believed by activists to be at least marginally effective against HIV and AIDS.

Wellcome’s announced pricing policy for AZT and the subsequent Congressional hearings served as a catalyst for the formation of the AIDS Coalition to Unleash Power (ACT UP), under the leadership of New York playwright and long-time gay activist, Larry Kramer. The group, made up of PWAs and supporters, was “united in anger to end the AIDS crisis” by channeling their frustration into “highly focussed, disciplined, and directed” actions, including acts of civil disobedience. ACT UP’s first protest action was a demonstration on Wall Street on March 24, 1987 involving 250 protesters who blocked rush hour traffic, distributed flyers condemning Burroughs Wellcome’s AZT pricing policy, and hung an effigy of FDA Commissioner Frank Young. However, the action garnered little media attention and no response from Burroughs Wellcome. Nevertheless, the protest inspired acts of civil disobedience by other AIDS advocacy groups in Washington, D.C. and San Francisco and led eventually to the formation of ACT UP chapters in Los Angeles, Boston, and Philadelphia by the end of 1987. ACT UP eventually adopted as its logo the phrase “Silence = Death” suspended on a black background under a pink triangle.

Price Cut for AZT

In December 1987, Burroughs Wellcome announced a 20% reduction in the price of AZT—from $1.88 to $1.50 per capsule—citing manufacturing efficiency improvements at Wellcome’s production facilities in Greenville, North Carolina and Dartford, England. In the news release, Burroughs Wellcome president and CEO Haigler stated, “We are delighted that the efforts of our production people and our suppliers have brought us to this point before we thought it would be possible.”

AIDS activists, however, were unimpressed with the price cut. In March 1988, ACT UP again staged a protest on Wall Street, resulting in the arrest of over 100 activists. Meanwhile, PWAs continued their love/hate relationship with AZT. Although providing dramatic health improvements for some AIDS patients, the 1200 mg. daily dosage destroyed so many red blood cells that many PWAs were forced to undergo blood transfusions several times a month or simply discontinue use of the drug. A small number of physicians reacted by prescribing lower dosages of AZT for certain patients. At the same time, many PWAs continued to experiment with unapproved drugs available through underground “buyer clubs.”

28 The pink triangle was a symbol used by Nazis to identify homosexuals in concentration camps during the 1930s and 1940s. By adopting this stark logo, ACT UP hoped to “force people to confront their own inaction towards [AIDS] and their own feelings toward gays.” Nussbaum, op. cit., p. 206.
29 Quoted in Nussbaum, op. cit., p. 189.
ACT UP and the FDA

In an attempt to pressure the FDA to approve some sixty experimental drugs for use by PWAs, ACT UP joined with a number of other AIDS activists to stage a massive demonstration at the FDA administration building outside of Washington, D.C. on October 11, 1988. Describing their protest as a "die-in," activists carried placards in the form of tombstones and traced outlines of bodies on the surrounding sidewalks, writing in the names of people who had died from AIDS. The over 1,000 protesters succeeded at shutting down the FDA and garnered substantial media attention. On October 20, the FDA published an interim rule designed to accelerate the approval process for drugs intended for previously untreatable, life-threatening diseases by eliminating the requirement of Phase III clinical trials for these drugs as it had already done with AZT. Later that year, FDA commissioner Young announced in a speech to AIDS activists that the FDA would not interfere with mail-order importation from overseas of any unapproved drugs for individual use.

Burroughs Wellcome Reaches Out

In late 1988, Burroughs Wellcome began to take a more active approach with respect to government affairs and public relations—activities still somewhat foreign to a firm that historically viewed itself as a research institution whose primary external constituency was the scientific and medical community. Burroughs Wellcome's low-visibility approach to AZT in particular could also be attributed to its parent company's decision to designate AZT as a special "chairman's project," which left all key decisions involving the drug in the hands of the London-based board of directors. Given the uneventful nature of AZT's approval and public reception in the U.K. market, there was no real counterpart in London to the controversy surrounding the drug in the U.S. market. Nevertheless, in December 1988, the company established a presence in Washington, D.C., hiring Richard Teske, former deputy assistant secretary of the U.S. Department of Health and Human Services, to represent Burroughs Wellcome to government officials and monitor political developments relevant to the firm.

In January 1989, Burroughs Wellcome agreed to meet with representatives of ACT UP at the company's headquarters to discuss the pricing of AZT. Although the activists were able to air their grievances in face-to-face meetings with Vice President Barry and members of the public relations department, they were unable to extract any price concessions from the company. Burroughs Wellcome, on its part, emphasized the complex array of cost factors underlying its pricing policy and noted that as soon as AZT had been approved, the company had created a program to provide AZT free of charge to indigent PWAs who had nowhere to turn for financial assistance. Although the program had indeed benefited several hundred people, ACT UP complained that it was completely unpublicized and arbitrarily administered.

In mid-April, ACT UP returned to Burroughs Wellcome headquarters, although this time uninvited. In an action designed to attract media attention, four activists dressed in business suits sneaked past Burroughs Wellcome security and sealed themselves in a third floor office with a high-powered drill. The activists then used a cellular telephone to conduct an interview with the Associated Press until police removed them from the building. Burroughs Wellcome, which felt that it had made a good faith effort to reach out to AIDS activists, was irritated by ACT UP's stunt, regarding it as childish and unproductive. In addition, as the only pharmaceutical firm having

30 Barry interview, op. cit.; O'Reilly, op. cit., p. 128.
31 Key information for this section was obtained in an interview with ACT UP/NY member Peter Staley, conducted on April 3, 1991.
developed an approved treatment for AIDS, the company found it particularly ironic that it should serve as a “punching bag” for activists’ ire.

Meanwhile ACT UP, in conjunction with other AIDS activist groups, sought new ways of exerting pressure on Burroughs Wellcome. One strategy involved an attempt to organize a consumer boycott of Wellcome’s leading over-the-counter drugs, Sudafed and Actifed. A second approach entailed renewed lobbying of Congress, particularly of Representative Waxman and other members regarded as sympathetic to the concerns of PWAs. Finally, the activist groups began studying possible strategies for challenging Burroughs Wellcome’s patent on AZT and its corresponding monopoly on the production and distribution of the drug. Although none of these strategies appeared to be particularly effective in the short term, activists hoped that with persistence, they would eventually begin to realize results.

**Regulatory and Scientific Developments**

In June 1989, AIDS activists claimed credit for two major regulatory developments. At the Fifth International Conference on AIDS in Montreal, Dr. Anthony Fauci, by then the key administrator of AIDS research programs at the NIH, endorsed the adoption of a “parallel track” testing procedure that would allow any PWA access to Investigational New Drugs during the clinical trial process without having to enroll as an official participant in the trials. With Fauci’s support, activists were confident that the FDA would sanction the principle of the parallel track within months, specifically in conjunction with the Phase II clinical trials for Bristol-Myers’s antiviral AIDS drug, DDI.32

In a second development later in June, the FDA granted marketing approval for the aerosolized delivery of the drug pentamidine for use in preventing the pneumonia PCP, the leading cause of death of people with AIDS. Of particular significance was the fact that research on pentamidine, a drug originally developed to treat sleeping sickness, had been conducted not by a large pharmaceutical company or government institutes, but by a network of community-based physicians. This marked the first time that an AIDS drug had been approved without placebo trials and the only instance in which a drug’s safety and effectiveness had been determined solely on the evidence provided by grass-roots clinical data. In spite of its effectiveness, aerosolized pentamidine posed no competitive threat to Burroughs Wellcome’s AZT. In fact, this second AIDS drug would presumably boost demand for AZT by prolonging the lives of PWAs who otherwise would have succumbed to PCP.

In August 1989, a development with even more significance to Burroughs Wellcome took place: Dr. Fauci announced to the national press that clinical trials33 measuring the effectiveness of AZT on HIV-infected persons with only mild symptoms or no symptoms of AIDS indicated that the drug appeared to delay the progression from HIV infection to AIDS in patients whose T4 cell count (a key indicator of immune system strength) had fallen below half the normal level.34 At the same time, Fauci revealed that the trials, which had also tested the impact of variations in drug dosage, showed that AZT was as effective and elicited fewer toxic reactions when administered at 500 mg. per day as opposed to 1200 mg. per day. At the reduced dosage, the percent of AZT users suffering from severe anemia declined from 30-40% to just 1%.

32 Even if DDI were to prove successful in Phase II trials, it was not clear whether the drug would become a complement to or a substitute for AZT. Hoffman LaRoche was also developing an antiviral AIDS drug, DDC, which was scheduled to enter Phase II clinical trials during the summer of 1989.

33 These trials were conducted by the NIH with the assistance of Burroughs Wellcome.

34 Such persons accounted for approximately 50% of the total HIV-positive, but AIDS asymptomatic, population. Barry interview, op. cit.
Although the recommended dosage for AZT was likely to fall almost 60% from its original level, Wellcome's stock price on the London exchange jumped 32% to £6.73 on the day following Fauci's announcement (see Exhibit 4). This response on the part of investors could be easily explained, however, by the tremendous increase in total demand for AZT expected as a result of the expansion of the potential market to include asymptomatic persons infected with HIV. Prior to Fauci's announcement, the number of AZT users in the United States totaled approximately 25,000 or about half of all PWAs (most of the others could not tolerate AZT). However, an estimated 1.5 million people were believed to be infected with HIV in the United States and millions more in other parts of the world.35 Given the rapid spread of HIV, these numbers were expected to rise dramatically in the 1990s. Yet it was unclear how many of these individuals were aware of their HIV status and both willing and financially able to take AZT.36 Nevertheless, some industry analysts projected that sales of AZT could reach $1 billion per year by 1992.37

**Pressures Mount on Burroughs Wellcome**

Although the FDA did not immediately sanction the use of AZT for all individuals infected with HIV nor lower the recommended dosage, it was expected that the agency would do so in the fall of 1989 as a result of the new clinical data. Meanwhile, AIDS activists and government officials watched to see how Burroughs Wellcome would react to the recent developments. Although the anticipated dosage reduction would, in effect, lower the annual retail cost per person of AZT to about $3300, ACT UP and others argued that Burroughs Wellcome should be willing to lower its unit price significantly, given the presumed explosion in demand for the drug. The company, however, remained silent and on September 5, representatives of fifteen leading AIDS activist groups traveled to Burroughs Wellcome headquarters to demand price cuts. Although Burroughs Wellcome personnel met with activists for some two and a half hours, no pricing concessions were offered. Before leaving, members of ACT UP warned that if Burroughs Wellcome did not give in to their demands, major demonstrations would be held against the company on Wall Street and elsewhere on Sept 14.38 The activists also threatened to organize a nationwide boycott of Wellcome products.

Meanwhile, additional pressure was brought to bear on Burroughs Wellcome. Representative Waxman wrote to Haigler, stating his belief that the high price of AZT was unwarranted given the level of government support received by the company in the development of the drug. Waxman also warned that he might reopen congressional hearings on AZT pricing. In a similar vein, NIH researcher Sam Broder, in interviews with the national media, alleged that Burroughs Wellcome had not given sufficient credit to government scientists in the process that ultimately led to the company's receipt of an exclusive patent for AZT. Finally, it was rumored that government lawyers were investigating the legality of a variety of punitive measures, ranging from price controls, to government manufacture of AZT, to the application of an obscure 1910 law that permitted the government to revoke patents where monopoly producer threatened strategic supplies.

As the target date of September 14 approached, ACT UP continued to develop its plan to infiltrate the New York Stock Exchange and intimidate, if not embarrass, Burroughs Wellcome into lowering its price for AZT. The effort was led by Peter Staley, a PWA and former Wall Street bond trader who had been taking reduced dosages of AZT long before Fauci's announcement, owing to the

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35 Nussbaum, op. cit., p. 316.
36 Since 1985, tests had been available for determining whether or not a person was infected with HIV. However, it was estimated that at most, only 20% of Americans with HIV had been tested as of late 1989. Barry interview, op. cit.
38 Staley interview, op. cit.
severe anemia he had suffered at the full recommended dose. The activists carefully studied the
NYSE through zoom lenses, obtained false trader badges through a Greenwich Village pawnshop,
and on September 11, carried out a "dress rehearsal" of the event at the Exchange itself. On
September 14, ACT UP's "direct action" was executed according to plan. Staley and his associates
were pleased with the extensive media coverage of the event, including a front page Wall Street
Journal story on September 15 under the headline: "Burroughs Wellcome Reaps Profits, Outrage from
Its AIDS Drug: Mounting Protests over the Cost of AZT Tarnish the Firm and Intensify Regulation."
The price of Wellcome common stock, which had fallen steadily after reaching £7.47 per share in
early September, closed at £6.74 on the London Stock Exchange on the day following the protests.

Formulating a Response

Burroughs Wellcome had weathered protests in the past and was extremely reluctant to set a
precedent of making "knee-jerk" concessions to activists. Furthermore, the company felt strongly that
it had fairly earned its AZT patent and pricing rights, in spite of the assistance it received during the
development period from governmental entities, which frequently provided services to other
pharmaceutical companies as well. Nevertheless, Wellcome PLC's Chairman Sir Alfred Shepperd
would expect to receive a clear recommendation within the next 24 hours from Burroughs
Wellcome's executive committee with respect to what strategy to adopt in response to the latest
round of demonstrations.
Appendix 1

Overview of Key U.S. Government Agencies Involved with AIDS

Most of the key scientific and regulatory agencies involved with AIDS in the United States were administered by an arm of the Department of Health and Human Services: the U.S. Public Health Services, chartered in 1912. Primary among these agencies were the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Centers for Disease Control (CDC).

National Institutes of Health (NIH)  Founded after World War II, the NIH, which was headquartered in Bethesda, MD, was a powerful directional force for U.S. medical research. The NIH not only disbursed government grants to universities—$4.6 billion in 1987 out of the NIH’s total budget of $6.1 billion—but also maintained eleven separate world class research institutes of its own, each specializing in a distinct disease class. Although the NIH’s spending on biomedical research was dwarfed by that of pharmaceutical firms, it was nevertheless regarded by the international medical research community as the “flagship” U.S. health research institution. Because of the complex manifestations of HIV and AIDS, two of the NIH’s institutes became involved in AIDS research: the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID). The NCI originally initiated AIDS research under Dr. Samuel Broder in response to the appearance of Kaposi’s sarcoma skin cancer in some AIDS patients in the early 1980s. The infectious nature of HIV itself elicited the eventual involvement of the NIAID under the leadership of Dr. Anthony Fauci. Although both of these institutes were part of the same agency, the issue of jurisdiction between the two over AIDS research was a delicate one, given the considerable sums of government research money earmarked for AIDS. By the late 1980s, it was clear that the NIAID had become the major site for AIDS research within the NIH.

Food and Drug Administration (FDA)  The Food and Drug Administration, located in Rockville, MD, was the key agency charged with regulating the drug approval process in the United States. The FDA and its predecessor agencies derived their authority from the Pure Food and Drug Act of 1906 and subsequent amendments to the Act adopted in 1938 and 1962. Over time, the FDA’s mandate with respect to drug regulation had expanded from insuring proper labeling to verifying both the safety and efficacy of each new drug prior to approval for sale to the public. In the 1980s, the FDA was regarded as the most stringent drug marketing approval agency in the world. The typical 10-12 year drug development and regulatory approval process (see Appendix 2) raised fears during the AIDS crisis that the FDA’s policies might actually cost lives by preventing promising drugs from reaching people with HIV/AIDS in time. These concerns were magnified by the apparent constraint on the FDA’s resources during the years of the Reagan administration: from 1981 to 1989 the agency’s budget rose a mere $49 million to $324 million in constant 1979 dollars, while its personnel declined from 7,900 to 7,350 over the same period.

Centers for Disease Control (CDC)  The CDC, located in Atlanta, GA, was a center of epidemiological study that tracked the spread of new and existing diseases. The agency, formally established in 1980 from a predecessor organization dating back to World War II, helped establish the linkage between the mysterious opportunistic infections that accompanied AIDS as part of a single disease syndrome. All health care entities throughout the United States were required to report to the CDC new cases of AIDS and deaths from AIDS on a regular basis.
Appendix 2

Overview of the Discovery and Approval Process for New Drugs in the United States

The search for a single commercializable drug in the 1980s typically started with the trial and error screening of some 10,000 compounds before testing the most promising of the substances in animals and humans. A significant portion of the total investment—one that consumed tens of millions of dollars and generated thousands of pages of supporting documentation—consisted of taking the drug through the U.S. Food and Drug Administration's exacting regulatory process. It was estimated that the average cost of developing a new drug (in current dollars) rose from $1.3 million in 1960 to $50 million in 1979 and topped $230 million by the end of the 1980s. A brief outline of the process appears below.

Initial Screening (1-2 years) During the initial screening stage, the thousands of compounds regarded as potential candidates for treating a specific medical condition were reduced to approximately 20 through chemical and structural analysis.

Pre-clinical Testing (2-3 years) Pre-clinical trials involved the testing of compounds in the laboratory and in animals to assess safety and to analyze the biological effects of each of the drug candidates. Approximately five of the compounds would subsequently be accepted as Investigational New Drugs (INDs) by the FDA for clinical testing in humans with respect to a specific indication (disease or other medical condition).

Clinical Testing (6 years) Clinical trials involved the testing of INDs in human volunteers. This stage of the process was divided into three separate phases:

- **Phase I Trials (1 year)** The Phase I safety trials in humans were designed to determine the safety and pharmacological properties of a chemical compound. Each drug was typically tested in 20 or more healthy volunteers. On average, 70% of all INDs moved on to the Phase II human trials.

- **Phase II Trials (2 years)** The Phase II efficacy trials were designed to evaluate the effectiveness of the drug and to isolate side effects. Tests were typically conducted with several hundred (volunteer) patients, half of whom received the IND and half of whom received a placebo. Only about one-third of all INDs survived both the first and second phases of clinical testing.

- **Phase III Trials (3 years)** The Phase III efficacy trials measured the effect of the IND on thousands of patients over several years. These trials helped ascertain long-term side effects and provided additional information on the effectiveness of a range of doses administered to a rich mix of patients. Approximately 27% of all INDs moved on to the FDA review stage.

FDA Review (2-3 years) Upon the completion of the Phase III clinical trials, firms were required to file a New Drug Application (NDA) with the FDA and submit documentation of all relevant data for review. The FDA created a special advisory committee for each NDA, typically approving the final recommendation of the committee as to whether or not the drug should be released for commercial sale. Post-marketing safety monitoring continued even after approval. Only 20% of all INDs ultimately made it through the full testing and approval stages.
Exhibit 1  Wellcome PLC: Five Year Financial Summary, 1985-89
(million £ except where otherwise indicated)

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<th>Fiscal Years Ending August 31</th>
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<td><strong>INCOME STATEMENT</strong></td>
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<td>Revenues:</td>
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<td>Human Healthcare</td>
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<td>Discontinued Ops a</td>
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<td><strong>Total Revenues</strong></td>
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<td>Taxes</td>
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<tr>
<td>Net Income</td>
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| **BALANCE SHEET** (Year end) |       |       |       |       |       |
| Current Assets           | 534.6 | 594.6 | 678.9 | 733.7 | 826.4 |
| Fixed Assets             | 356.8 | 392.0 | 446.9 | 522.3 | 592.2 |
| Total Assets             | 891.4 | 986.6 | 1125.8| 1256.0| 1418.6|
| L.T. Debt                | 164.6 | 164.1 | 186.4 | 181.3 | 168.5 |
| Equity Capital           | 438.6 | 513.6 | 559.0 | 652.6 | 821.2 |
| Total Capitalization     | 603.2 | 677.7 | 745.4 | 833.9 | 989.7 |

| **RATIOS AND SHARE DATA** |       |       |       |       |       |
| Gross Margin             | 66.1% | 67.5% | 68.2% | 70.6% |       |
| Return on Sales          | 5.6%  | 6.1%  | 8.6%  | 10.5% | 12.2% |
| Return on Equity         | 13.6% | 12.4% | 16.8% | 19.5% | 20.2% |
| Dividends/Earnings       | 28.0% | 27.2% | 25.2% | 23.2% | 23.6% |
| Shares Outstanding (m)   | 800   | 824   | 843   | 844   | 845   |
| Share Price: High        | £2.34 | £5.14 | £5.70 |       |       |
| Low                      | £1.56 | £1.78 | £2.92 | £4.00 |       |
| Avg £/$ Exchange Rate    | 1.23  | 1.46  | 1.55  | 1.76  | 1.68  |

aCoopers Animal Health—nine months results included for 1989.
bNot available.
cShares were not issued to the public until 1986.

Exhibit 2  Wellcome PLC: Revenues by Product Group, 1985-89

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<th>Fiscal Years Ending August 31</th>
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<td>(percentages)</td>
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Exhibit 3  Reported U.S. Cases of AIDS and Deaths Attributed to AIDS: 1981-89

![Graph showing reported U.S. cases and deaths attributed to AIDS from 1981 to 1989.]


![Graph showing monthly closing price of Wellcome stock on the London Stock Exchange from September 1986 to August 1989.]