A History of Accelerated Approval: Overcoming the FDA's Bureaucratic Barriers in order to Expedite Desperately Needed Drugs to Critically Ill Patients

A History of Accelerated Approval: Overcoming the FDA's Bureaucratic Barriers in order to Expedite Desperately Needed Drugs to Critically Ill Patients

Jacob W. Stahl, Class of 2005

Harvard Law School

March 31, 2005

Submitted in Satisfaction of Food & Drug Law and Third Year Paper Requirements

Professor/Advisor: Mr. Peter Barton Hutt

ABSTRACT

After the passage in 1962 of the Kefauver-Harris Drug Amendments that mandated that the FDA grant premarket approval for all drugs and added a requirement that drug manufacturers demonstrate the efficacy of their products, the drug approval process dramatically slowed for the next two decades. Only after a combination of sustained criticism by free market advocates and dramatic lobbying efforts and protests by AIDS activists desperate for any drug that might prolong their lives did the FDA relent and implement the accelerated approval program. The FDA can grant accelerated approval for drugs designed to treat life-threatening diseases for which no approved treatments currently exist based upon data from surrogate endpoints (laboratory markers), so long as the endpoints are reasonably believed to predict clinical benefit. This paper examines the history of accelerated approval, and in particular its application to AIDS and cancer drugs. Additionally, it explores critiques of the program from clinical academicians and consumer advocates, and replies from its defenders including the pharmaceutical industry, patient advocates and free market economists. It concludes with recommendations on how to reinvigorate the process in order to expedite the development of cancer drugs.

I. INTRODUCTION

Though much of the past half century, there has been a raging battle between proponents of two competing paradigms of drug approval. On the one side stand many members of Congress and self-styled "consumer" advocates who decry the FDA ("the Agency") for being too lax in enforcing safety and efficacy requirements. On the other stand a coalition of free market economists and patient advocates who condemn the FDA for being needlessly slow and overcautious. While the Agency proclaims that it is protecting public heath by demanding voluminous safety and efficacy data before approving a drug, it is in fact causing grave harm by needlessly denying patients drugs that could save their lives, cure their illnesses, and/or dramatically ameliorate their symptoms.

Nowhere has this debate taken on more urgency than in dealing with drugs for patients suffering from diseases for which there is no known cure, such as AIDS and many forms of

cancer. Under pressure from AIDS activists, the FDA in 1992 implemented a process called "accelerated approval" for expediting the regulatory process for drugs designed to treat life-threatening diseases for which there is currently no adequate treatment. Briefly, in order to secure accelerated approval, a drug manufacturer does not have to meet the usual requirement of demonstrating actual clinical improvements (such as improved longevity) in a full-scale clinical study. Rather, the manufacturer need only show an effect on a surrogate endpoint, a laboratory measurement that can be determined relatively easily over a short time, so long as the surrogate endpoint is believed reasonably likely to predict clinical benefit.

This paper examines the history of the accelerated approval regime, originating with the backlash of free market economists in the 1970s and 1980s against the FDA's sclerotic drug approval process, and augmented by immense political pressure placed on the Agency by frantic HIV/AIDS activists who, fearing a virtual death sentence, demanded that new drugs be placed on the market as quickly as possible. As pressure from AIDS activists lessened because of the development of treatment cocktails that have done a reasonably good job of treating that disease, the FDA began facing pressure from both Congressional Republicans eager to expedite the entire drug approval process and cancer activists demanding that oncology drugs be given equal treatment to that of AIDS drugs. Consequently, the Agency began granting accelerated approval for cancer drugs as well and has continued doing so for almost a decade. Yet, this has recently been met with a backlash of FDA staff and clinical academicians, in concert with consumer groups such as Public Citizen, who fear the Agency has been approving ineffective drugs with unacceptable levels of toxicity. The history of the accelerated approval process thus can be described as the story of a highly risk-adverse regulatory agency that has yielded to demands to

act more expeditiously under the weight of unyielding political pressure, but rapidly reverts to its cautious ways whenever it comes under criticism from Congress and consumer groups.

Part II of this paper examines the historical origins of the accelerated approval process, including the development of the FDA's cautious culture in the 1960s, the criticisms by free-market economists in the 1970s and 1980s, and the desperate attempt by AIDS patients to get hold of any compound that held out the slightest possibility of efficacy. This section also details the Agency's first feeble attempts to expedite new drugs to the market and the Lasagna report that would served as the intellectual underpinnings of the accelerated approval process. Part III provides an in-depth examination of the regulations themselves, as understood by the FDA when they were implemented in 1992. Part IV examines the application of the accelerated approval process to AIDS drugs, beginning with the nucleoside inhibitors, the subsequent backlash by some AIDS activists concerned that new drugs were being approved based upon shoddy data, and culminating in accelerated approval of protease inhibitors and the development of treatment cocktails. Part V details the pressures brought upon the Clinton Administration to extend accelerated approval to cancer drugs. This section also details the backlash against the pharmaceutical industry during the late 1990s and the FDA's reversion to being highly cautious. Part VI explores efforts by Chairman Mark McClellan to create economic incentives to stimulate drug development that included proposals to facilitate the accelerated approval process. Part VII examines two of the most controversial anti-cancer drugs that have been examined by the FDA, Iressa and Marqibo. This analysis provides significant insights into the FDA's current thinking on accelerated approval. Part VIII presents differing perspectives on the accelerated approval program. Included are condemnations of the program from clinical academics, a reply from Dr.

Antonio Grillo-Lopez of the pharmaceutical industry, and the views of an informed cancer survivor on the best way to improve the cancer treatment process. Finally, Part IX provides recommendations for combating cancer by utilizing the accelerated approval process as a means of providing economic incentives for manufacturers to create as many new treatments as possible and then facilitating efforts both by practicing physicians and clinical researchers to develop treatment cocktails that represent the best hope for treating the disease.

II. HISTORY OF NEW DRUG APPROVAL PROCESS

A. Origins of the FDA slow-down in Drug Approval

1. The Federal 1938 Food, Drug, and Cosmetic Act

The two most significant pieces of drug-regulation legislation were both spurred by tragedies resulting from the introduction of unsafe drugs. Until the passage of the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), there was no comprehensive regulatory scheme for new drugs in the United States. From 1933 to 1937, Congress had been debating the possibility of giving the FDA additional authority to regulate drugs, but without requiring any form of premarket review. Congress finally acted in 1938, after the Elixir Sulfanilamide tragedy, which occurred when the Massengill Company marketed sulfanilamide with diethylene glycol as a solvent. As a result, one hundred people were poisoned. Under the 1938 Act, manufacturers were required to provide limited premarket notification of the safety of a drug to the FDA in the form of a new drug application (NDA). The Agency was given 60 days after filing (which could be extended to 180 days) to act on the NDA; if it failed to act, the drug could be marketed. Section 505(d) of the FDCA mandated that the FDA reject any drug for which (1) adequate safety tests were not performed; (2) the results of the tests demonstrated that the drug was unsafe or (3) the methods used in manufacturing the drug were inadequate to preserve the drug's "identity, strength, quality and purity." The Act also required that drug manufacturers comply with investigational new drug (IND) regulations before they could test a compound on humans. However, the FDCA did not contain any efficacy requirements.

2. The Kefauver-Harris Drug Amendments of 1962 and the Modern Drug Approval Process

The 1938 Act was significantly strengthened in 1962 after the Thalidomide catastrophe in Europe in the early 1960s. Thalidomide was marketed in Europe for treatment of pregnancy-related illnesses for women, but unfortunately it was also a tetarogen that caused horrific birth defects in thousands of babies. However, Dr. Francis O. Kelsey of FDA refused to allow the NDA to become effective because of safety concerns, and consequently Thalidomide was not marketed in the Untied States. Nonetheless, because of the ensuing public outcry, Congress passed the Kefauver-Harris Drug Amendments of 1962. Under the 1962 Amendments, the old system of premarket notification was replaced with a new requirement that the FDA grant affirmative premarket approval before a drug could be sold. Additionally, the Amendments required that the manufacturer demonstrate the effectiveness of any new compound.

Based upon the 1962 Amendments, the FDA promulgated the standard of research required to support a NDA. In order to receive the IND necessary to begin human testing, a sponsor must detail both a plan for human research and known data on the compound including human experiences with the drug and animal toxicology studies. If the IND is not rejected, then the sponsor is generally required to go through three phases of clinical investigation. Phase I involves a study on a small number of volunteers, and is designed to examine the pharmacological effect on humans. The goal of Phase I trials is to determine the appropriate dosages, avoid toxicity and possibly learn about the drug's effectiveness. Phase II consists of a controlled study of a few hundred patients who are closely monitored in order to further evaluate

the effectiveness of the drug and to determine side-effects. Phase III trials are designed to make a dispositive determination of the drug's efficacy, and therefore usually consist of large, randomized controlled trials (RCTs). The FDA normally requires two such studies; the control does not have to be a placebo. The data from these trials are submitted to the FDA in the form of a NDA. If the data demonstrates that the drug is safe and effective, the NDA should be approved by the Agency.

3. Congressional Attacks on the FDA

Beginning in 1963, Senator Hubert H. Humphrey launched a series of oversight hearings relating to the FDA's implementation of the 1962 Act, commencing a fifteen year Congressional crusade to highlight the dangers of drugs that allegedly were ineffective and/or unsafe. The next year, Congressman L.H. Fountain began his own series of hearings that would last for many years in which he expressed similar concerns. In 1974, Senator Edward Kennedy jumped into the fray, conducting hearings at which he contended that the FDA was improperly influenced by the pharmaceutical industry and that consequently the Agency was letting unsafe and ineffective drugs onto the market. Senator Kennedy has been sniping at the FDA ever since.

B. Backlash against An Over-Zealous FDA: Free Market Economists

By 1972, commentators began warning that the FDA was unnecessarily obsessed with safety. In February of that year, Dr. Robert Dripps, Vice President for Medical Affairs at the University of Pennsylvania wrote a letter to Congress (signed by twenty-one other scientists) warning that the United States was falling behind the rest of the world in medical science.

Shortly thereafter, Dr. William M. Wardell argued that the United States was suffering from a "drug lag," meaning that the FDA's bureaucratic delays were causing new drugs to be introduced onto the market in the US much more slowly than elsewhere in the world (an argument many continued to make for the next two decades).

In 1973, Professor Sam Peltzman testified that the 1962 Amendments resulted in twenty-five new chemical entities less entering the market each year, and that the FDA's new requirements had approximately doubled the research and development costs for new drugs. Furthermore, the lost benefits were not outweighed by the savings from avoiding ineffective or dangerous medicines. That same year, Professor Peltzman wrote an article in which he concluded by pondering why these regulations, which harmed consumers without providing offsetting benefit to producers, would continue to survive.

The following year, when Senator Kennedy launched his hearings discussed above, the FDA was equipped with a reply. Commissioner Alexander Schmidt stated:

> [I]n all of DA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them . . . The message to FDA staff could not be clearer. Whenever a controversy over a new drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made.

In subsequent years, the FDA faced continued criticism for its inaction. In 1976, the President's Biomedical Research Panel issued a report declaring that the FDA had become a "formidable roadblock" in the path of developing new drugs, with its lengthy requirements constituting a "hazard to public health." That same year, Dr. David Schwartzman, Professor of Economics at the New School for Social Research, issued a report stating that the expected rate

of return in the pharmaceutical industry was below the level necessary to sustain new drug investment. He furthermore concluded that the charges levied against the pharmaceutical industry during the previous decade of Congressional hearings were unfounded.

In July 1979, Congress held its first hearing on the complaint that the FDA was in fact too cautious. The hearing was held by the Subcommittee on Science, Research and Technology to investigate the findings of a GAO report, requested by Congressman James H. Scheuer, on the effectiveness of the FDA. At the hearing, the GAO confirmed that there in fact was a drug lag created by the FDA's lethargic drug approval process.

After largely unsuccessful efforts to reform the FDA during the Reagan administration, free market proponents renewed their criticisms of the FDA in the late 1980s and early 1990s in light of the AIDS crisis. In 1990, Sam Kazman wrote an article building upon Professor Pelzman's work, in which he argued that the FDA's extensive requirements, which necessitate NDAs in excess of 100,000 pages, keep valuable drugs off the market, leading to the deaths of people that could have been saved had these drugs been available. One example that Katzman cited of "overcaution [being] deadlier than caution" pertains to the Agency's handling of beta blockers, medication designed to prevent heart attacks. Although former FDA Commissioner Donald Kennedy defended the Agency's ten year delay by arguing that it was necessary to ensure that the drug was not tumorigenic, Katzman cites Dr. Wardell who noted that introducing the drugs could have saved ten thousand people a year with relatively few side effects. According to Dr. Wardell, "These important advances are what Dr. Kennedy triumphantly takes credit for 'protecting' us from; the concept of risk avoidance has been turned pyrrhically on its head." Kazman contended that from the FDA's perspective, the discovery that beta blockers caused

tumors in a small number of patients would have subjected it to embarrassment at Congressional hearings, whereas it faced little political repercussions from the thousands of people who would still have been living had the beta blockers been approved. Kazman argued that because peoples' risk tolerance varies, the FDA should put relax the standards for drugs being put on the market and let patients and their doctors make an individualized risk-benefit assessment.

C. AIDS Activists, the FDA and the Lead-up to Accelerated Approval

On June 5, 1981, the Centers for Disease Control (CDC) reported that five gay men in Los Angeles had contracted *Pneumocystis carinii pneumonia* (PCP), a rare disease. One month later, the *New York Times* ran an article stating that forty-one gay men had contracted Kaposi's sarcoma, an unusual form of cancer. By the fall of that year, scientists recognized that they were contending with a mysterious new disease, originally known as Gay Related Immune Deficiency (GRID); the CDC latter called it Acquired Immune Deficiency Syndrome (AIDS).

In 1983, research groups headed by Robert Gallo and Luc Montagnier discovered that AIDS was caused by a retrovirus (human immunodeficiency virus [HIV]) that attacked T4 lymphocytes (otherwise known as CD4 cells), a form of immune cells that are required for a proper immune response. Once HIV significantly weakens the immune system, patients are susceptible to opportunistic infections and specific forms of cancer. According to the CDC, AIDS is defined as when a person has fewer than 200 CD4 positive T cells per cubic millimeter of blood (as opposed to 1,000 or more in a healthy person) or if they have one of twenty-six opportunistic infections. AIDS is usually transmitted through unprotected sex with an infected partner or through contact with infected blood. Because there were no known drugs or

treatments for HIV or the opportunistic infections that it spawned, it initially amounted to a virtual death sentence to many of those that were infected.

Initially, the gay community reacted to AIDS with complete despair. People With AIDS (PWAs, as they came to be known) spoke of "beautiful death," "journeying to the other side" or "surrendering Earth's sorrow." However they were unable to mount sufficient political pressure to mobilize a massive research effort to develop AIDS treatments; President Ronald Reagan refused to ask Congress to allocate money for AIDS research. Because there were no approved AIDS treatments, PWAs rapidly turned to quack medications such as processed T-cells, injecting bovine fetal tissue and bathing in chlorine bleach. Additionally, many turned to smuggling rings to import drugs from Mexico that were reputed to treat AIDS, but were not approved by the FDA. In 1987, it was estimated that PWAs were spending more than one billion dollars annually on worthless AIDS treatments.

Meanwhile, AIDS activist began developing groups to lobby for AIDS research. One of the first to form was the Gay Men's Health Crisis, founded in 1981 in New York City to provide education, support and counseling for PWAs. Over time, as frustration mounted with the slow pace of drug approval, AIDS activists became more militant. On March 10, 1987, Larry Kramer gave a fiery speech at the Lesbian and Gay Community Services Center at which he asked two-thirds of the two-hundred and fifty people present to stand, and then he exclaimed, "At the rate we are going, you could be dead in less than five years . . . If what you're hearing doesn't rouse you to anger, fury, rage and action, gay men will have no future here on earth." Two days later, ACT UP was formed, and they adopted the motto: "Silence=Death." ACT UP performed numerous publicity stunts to raise the profile of their cause. Their most notable event occurred

on October 11, 1988 when 1,000 protesters descended upon the FDA's headquarters, some chaining themselves to the Agency's front door, shouting "Arrest Frank Young" (then FDA Commissioner). Others lay on the ground holding signs reading, "Rest in Peace, Killed by the FDA."

In February 1985, scientists discovered the first promising AIDS treatment. Researchers at the National Cancer Institute (NCI) determined that a molecule that researchers at Burroughs Wellcome (BW) called Compound S, which was known as azidothymide or zidovudine—soon to be called AZT—was able to kill HIV in a test tube. AZT was the first of a class of nucleoside reverse transcriptase inhibitors. These drugs attempt to stop the HIV virus early in the viral cycle by interfering with reverse transcriptase, a viral enzyme that normally converts viral RNA into viral DNA. Viral DNA is required for viral replication; this process can be stopped by inhibiting reverse transcriptase.

In June of that year, BW filed an IND with the FDA. Because reports of its success were so promising, the FDA approved the IND within a week and Phase I testing began soon thereafter. The drug appeared not to be toxic and patients appeared to have some clinical improvement. In June 1986, 282 people were put on Phase II tests, and six months into the trial, the patients on AZT were doing so much better than those on placebo that all the patients were offered the active drug. Shortly thereafter, BW offered free AZT to 4,500 PWAs on a compassionate use basis. Although the FDA had doubts about the safety and effectiveness of AZT, its NDA was nonetheless approved in March 1987—a remarkably short amount of time by Agency standards.

In 1987, the FDA launched its first initiative to speed AIDS drugs to the market, a

program known as “treatment INDs.” Under this program, certain drugs for life-threatening illnesses could be sold after Phase I, but only if research on the drugs continued, and the drugs were shown to be neither unreasonably dangerous nor ineffective. Although many AIDS activists supported the program, some did express concerns that dangerous drugs were unknowingly be placed on the market. Some prominent researchers worried that once drugs were on the market, patients would no longer risk joining a study whereby they might receive a placebo. Additionally, five former FDA commissioners expressed concern that treatment INDs were gutting the efficacy requirements of the 1962 Amendments. The FDA published its final rule in the Federal Register on March 22, 1987, stating that treatment INDs could be granted for drugs treating “immediate or life threatening” so long as there was proof that the drug “may be effective.” Although treatment INDs had engendered significant political conflict, two commentators wrote that they had done little more than to codify the FDA’s compassionate use program. Likewise, John S. James, a prominent lay commentator and author of an influential AIDS newsletter since 1986, complained that the FDA was applying treatment INDs very conservatively, only approving them towards the end of efficacy trials.

Because of concern that treatment INDs were not succeeding in getting new drugs to PWAs, in March 1989 Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (the government body charged with researching AIDS) announced a new program called “parallel track.” Under this program, patients with life threatening illnesses who could not join a study, because they were ineligible, they were too far away, or the study was full, could nonetheless receive the experimental drug. Officials at the FDA, who lacked advanced warning of Fauci’s speech, were upset by the proposal because they believed that treatment

IND's were sufficient to get experimental drugs onto the market. However, as described above, many AIDS activists were distrustful of treatment INDs, and demanded the FDA act more aggressively. Ultimately, James Mason, Assistant Secretary for Health, who was in charge of both FDA and NIAID, relented. An announcement of proposed parallel track regulations for HIV/AIDS was put into the Federal Register on May 21, 1990.

Long before the parallel track was officially implemented, the concept was invoked to speed a new anti-AIDS drug, ddI, to market. Scientists believed that ddI acted similarly to AZT, but they hoped that it would have fewer side effects. Moreover, they hoped that the drug would prove beneficial to patients who had become resistant to AZT. In September 1989 AIDS activists demanded that ddI be supplied immediately even though it had not yet been approved by the FDA. Larry Kramer declared, "If we do not get these drugs, you will see an uprising the likes of which you have never seen before since the Vietnam War in this country." AIDS activists eventually got their wish; at the end the month, the government announced that it would be making ddI widely available through a parallel-track type mechanism despite long term toxicity testing on less than one hundred patients. Under the arrangement reached with the FDA, three AIDS Clinical Trial Group (ACTG) trials would be held; two would compare ddI to AZT. A third trial, reserved for patients resistant to AZT, would compare different dosage levels of ddI. Simultaneously, patients ineligible for the trials or who had developed adverse reactions to AZT could be supplied with ddI.

Although the parallel track was the source of heated debate, it ultimately did not have a significant impact. Besides ddI, which was approved before parallel track, the only drug that was made available under it was stavudine (d4T). Parallel track has largely been superceded by

accelerated approval. The story of AIDS and accelerated approval will be discussed in depth at Part IV, infra.

C. The National Committee to Review Current Procedures from Approval of New Drugs for Cancer and AIDS (Lasagna Commission)

Amidst the efforts of AIDS activists to prod the FDA into faster action, the National Committee to Review Current Procedures from Approval of New Drugs for Cancer and AIDS (Lasagna Commission) released its final report that reflected many of the demands of AIDS activists and recommended implementing what would come to be known as accelerated approval. Vice President George H.W. Bush, as chairman of President Ronald Reagan's Task Force on Regulatory Relief, commissioned the report, and the panel was headed by Dr. Louis Lasagna, Dean of the School of Graduate Biomedical Sciences at Tufts University. The panel was charged with "undertak[ing] a systematic study of drug regulation as it affects progress in developing and making available therapies for cancer and for AIDS, and mak[ing] recommendations for improvements. This study could include . . .changes that, while preserving protection for patients, would accelerate the conduct of clinical trials . . . ."

In the Introduction to the report, the authors presented the view of free-market economists and AIDS activists that the FDA approved drugs too slowly. According to the report, "Patients suffering from [cancer and AIDS] cannot afford the luxury of waiting for drug development and regulation to move as slowly as they usually do . . . .[T]ime is running out and they are understandably impatient with delays in obtaining the pharmacotherapy which represents their only hope." The Commission observed that because medications for the terminally ill are at the "cutting edge of modern science, "the FDA should express more

"flexibility . . . .with a willingness to change protocols, dosage and dosage regimens promptly . . . and take a positive attitude toward such innovation."

One significant recommendation of the Lasagna Commission was the need for a multiplicity of AIDS and cancer treatments because, "[T]here are numerous subpopulations, each of which has its own characteristics, limitations, and needs with respect to drug therapy." Although this observation might sound obvious, it would prove to foreshadow the debate over "availability" that arose in the context of the FDA's rejection of Marqibo, as discussed in Part VII(B), infra.

The Lasagna Commission also criticized a high efficacy threshold, echoing Katzman's concerns that it had needlessly slowed down the drug approval process. Arguing that terminally ill patients, in consultation with their doctors, should be able to elect to assume a higher level of risk, the Commission cited the Senate Report on the 1962 Drug Amendments, which stated, "In such a delicate area of medicine [where there is a difference of opinion as to whether or not the drug is effective], the committee wants to make sure that safe new drugs become available for use by the medical profession so long as they are supported as to effectiveness by a responsible body of opinion and scientific fact." The Commission therefore contended that the FDA should not be the ultimate arbiter of effectiveness, but rather should leave the patients the option of taking risky treatments if they would otherwise likely die. For this reason, it proposed modifying the efficacy standard in the case of terminally ill patients by approving drugs based upon Phase II data. They reasoned that Phase III trials were unnecessary for purposes of approving the NDA because Phase III trials frequently involve active controls that are used to demonstrate *superiority* (comparative efficacy) of the given drug, whereas mere efficacy can be determined in

Phase II trials.

The Commission urged that manufacturers be permitted to submit Phase II data using surrogate endpoints. Traditionally, studies are measured based upon the length of survival, the classical clinical endpoint. However, the Commission argued that in the case of slow growing tumors, it would be both "impractical and unethical" to use survival as an endpoint, especially because most cancer drugs cannot extend longevity alone, but rather only work in combination with other drugs. Therefore, the Commission suggested that cancer trials be analyzed based upon the surrogate endpoint of twenty to thirty percent tumor reduction, because in ninety percent of cases, anti-cancer drugs that demonstrated activity in Phase II trials prove to be clinically effective in Phase III trials. Approving drugs at this early stage would permit physicians to use their discretion to arrange a treatment regimen of anti-cancer medications most likely to have the desired effect. The Commission likewise urged that CD4 counts should be used as a surrogate marker for AIDS.

III. Enactment of Accelerated Approval Regulations

A. The FDA's Presentation of Accelerated Approval/Subpart H Regulations

On April 15, 1992, the FDA submitted a notice to the Federal Register proposing the accelerated approval program; a final rule was issued on December 12, 1992. The regulations implementing the program are found under 21 CFR part 314, under subpart H, consisting of §§314.500 though 314.550.

In its opening comments to the proposed rule, the FDA detailed almost a decade worth of efforts to expedite approval of drugs for patients with life-threatening illnesses, including programs like treatment INDs and parallel track. Yet, they observed that more reform was to ensure the "approval of new drugs for treatment of these diseases at the earliest time permitted under the law."

These regulations first required that the drug be designed to treat serious or life threatening diseases, defined as illnesses that impact day to day functioning, or are assumed to threaten survival if left untreated. Included in this definition were HIV/AIDS, heart failure, and cancer. Also included were chronic diseases that can often be controlled but can have severe consequences such as inflammatory bowel disease, diabetes mellitus and asthma.

The second requirement was that the drug provide a "meaningful therapeutic benefit over existing therapy," defined as where "a serious medical need is not met by currently available therapies." Thus the regime could apply to cases where patients were either non-responsive to, or intolerant of, the old treatment or if the new drug was more effective and/or had fewer side effects. However, the FDA warned that it would not grant accelerated approval if it believed that the primary use for the drug would be for a non-life-threatening or non-serious illness.

The third requirement pertained to surrogate endpoints. The FDA defined surrogate endpoint as "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy." All surrogate endpoints, however, are not created equal, because the causal relationship between surrogate endpoints and clinical outcomes varies along a spectrum. At one end were verified surrogate endpoints that have frequently been utilized by the FDA for granting regular approval. For example, high cholesterol or high blood pressure (hypertension) do not impact how a patient feels, but are significant risk factors for heart disease and stroke, so lowering these variables had long served as acceptable data for the purposes of granting approval. However, the FDA noted that some surrogate endpoints can reflect spurious correlation. For example, people with pneumonia frequently have fevers, but a fever cannot serve as a surrogate endpoint because a fever can be lowered while the pneumonia remains. The FDA stated its willingness to grant accelerated approval when there is "basis of an adequate and well-controlled trials establishing that the drug has an effect…that is *reasonably likely* (based on epidemiologic, therapeutic, or other evidence) to predict clinical benefit."

Fourth, drug manufacturers were required to perform postmarketing (Phase IV) studies to verify the clinical benefit predicted from the surrogate markers. These studies were usually the type submitted with the traditional NDA. The FDA stated its expectation that these trials usually be underway at the time of application and be conducted with "due diligence."

The Agency reserved the right to impose postmarketing restrictions on distribution of the drug should it fear that the risk of toxicity is so high that even labeling is insufficient. For

example, the FDA could limit distribution of the drug to doctors with special training, such as those having the capability to deal with dangerous side effects. Alternatively, the FDA could require that doctors only distribute the drug if they comply with certain medical procedures, such as a regime of blood tests. It should be noted that the FDA stated its intent to use distribution restrictions only "rarely and in extraordinary cases."

As part of the accelerated approval regulations, the FDA also announced a procedure for streamlined withdrawal if the postmarketing study did not demonstrate the anticipated clinical benefit, if the drug's sponsor failed to carry out the postmarketing study with the required due diligence, or if the postmarketing restrictions were inadequate or were violated by the manufacturer. The FDA argued that it should be permitted to withdraw the drug if Phase IV data is unfavorable because without clinical improvement, then there is no benefit to counteract any toxicity caused by the drug.

When the FDA issued its final rule, it did not change any of the regulations that it originally imposed. It only added one slight modification, namely that it would terminate the expedited withdrawal provision should Phase IV data demonstrate clinical effectiveness, and the restrictions on distribution would terminate upon determination that proper labeling was sufficient to ensure safe use of the drug.

B. Reaction to Accelerated Approval: Questions and Answers in the Final Rule

Some of the comments and replies printed by the FDA's final rule in the federal register are instructive because they analyze many of the issues that repeatedly have arisen when the FDA has considered granting accelerated approval to specific drugs.

First, some were concerned that granting approval based upon surrogate endpoints violated the "substantial evidence" requirement of §505(d) of the FDCA because in absence of a verified surrogate endpoint or a clinical endpoint, a surrogate endpoint is nothing more than a "hypothetical construct." The Agency responded that the Act required a "clinically meaningful outcome," a relative standard based upon a risk/benefit analysis. This would not be a lower standard of evidence, but rather would reflect an assessment that given the gravity of the disease and the credibility of the surrogate endpoint, the benefits outweighed the risks.

Second, some feared that the accelerated program might just lead to approval of drugs which are pharmacologically active but clinically worthless, a situation detrimental to public health. The FDA responded that it believed that if a manufacturer complied with all the requirements of the accelerated approval process, then its drug would likely prove beneficial because altering a surrogate endpoint reasonably likely to predict clinical benefit is a far higher standard than pharmacological activity. Moreover, the Agency still reserved the right to withdraw the drug from the market on an expedited basis should the Phase IV results prove inadequate. Furthermore, the FDA rejected the concern that relying upon surrogate endpoints would become the "normal" way that drugs are approved because most drugs address short term conditions that lend themselves to rapid measurements of clinical response.

Third, several commentators worried that once granted accelerated approval, manufacturers would no longer have the incentive to participate in postmarketing studies, especially if the current data demonstrated the drug to be safe and effective. The FDA, however, downplayed the risk because of the requirement that Phase IV studies be underway at the time that accelerated approval is granted. Moreover, the Agency maintained the right to withdraw

accelerated approval should the manufacturer not proceed with sufficient diligence.

Fourth, several expressed fears that once a drug was approved, it would be unethical to use placebo controls in trials. In response, the FDA observed that placebo controls were not required, because active controls and/or dose response studies can satisfy both safety and efficacy requirements.

Fifth, commentators expressed conflicting fears on the withdrawal provisions. On the one hand, one expressed concern that if a drug only had a modest impact on a surrogate endpoint and the clinical benefit was unclear, in the absence of data indicating it was highly toxic, it would be politically unfeasible to withdraw it. On the other hand, another commentator worried that the FDA might withdraw a drug that was not effective in the overall population but was indeed beneficial in a subpopulation. Likewise, another suggested that patients should be able to give informed consent to using a drug even if there were questions about safety and efficacy. In response, the FDA stated that it would at least consider withdrawing a drug on the basis of inconclusive data. Moreover, to the extent that a study failed to prove benefit because it was poorly designed or implemented, the Agency pledged to do everything possible to ameliorate the situation but warned that ultimately the manufacturer was responsible to confirm clinical benefit. Although the Agency never replied to the concern that withdrawal would be unfair, it presumably would have replied that it was statutorily obligated to keep drugs off the market that were unsafe and/or ineffective, despite patient requests to the contrary.

C. Post-Script: Codification of Accelerated Approval in 1997

In 1997, after a protracted debate, Congress passed the Food and Drug Administration

passed the Food and Drug Administration Modernization Act (FDAMA). Although the Act did not contain any dramatic changes that mandating that the Agency expedite the regulatory approval process, §112 did codify the accelerated approval process (known in the bill as "fast track.") As a related matter, Congress altered the effectiveness standard by giving the FDA explicit permission to approve a drug on the basis of one quality controlled study. However, this change merely codified the status quo because the FDA had previously approved certain drugs on the basis of similar data.

IV. AIDS and Accelerated Approval

A. The Opening Act: FDA's Decision to Use CD4 Counts as Surrogate Endpoints

In February 1991, a year before the accelerated approval regulations were implemented, an FDA Advisory Committee recommended utilizing CD4 counts as surrogate markers. This decision took place under the backdrop of AIDS activists clamoring for a greatly expedited drug approval process. In June 1989, John S. James bemoaned the fact that the only drug approved to treat AIDS was AZT, which unfortunately did not work in some patients. He expressed dismay that several promising drugs such as ddI, ddC, and d4T were not expected to be approved for several years. James blamed these slow trials on the demands of researchers for data on the number of deaths or opportunistic infections, a result that could take years to develop. Martin Delaney, executive director of Project Inform, a group representing AIDS patients, likewise criticized the conventional studies for being "body count trials" which were infeasible for AIDS patients who refused to stay in a long-term trial while new drugs entered the market.

James and other AIDS activists (in addition to the Lasagna Commission) recommended using surrogate markers, which could significantly accelerate data collection. CD4 counts were viewed as the surrogate marker most likely to predict clinical outcome. Some scientists theorized that since CD4 cells are attacked by the AIDS virus and patients worsen as CD4 counts drop, raising CD4 counts should result in clinical benefit. In one of the studies presented at the FDA Advisory Committee meeting that examined AIDS patients on AZT, CD4 counts did appear to predict duration of survival.

However, many scientists were skeptical of claims that CD4 counts were correlated with clinical benefits. According to Richard Johnson Jr., a pediatrics professor at the University of

Pennsylvania, "[T]here is no good evidence to show that if you prop up or stabilize CD4 counts, especially by immunologic means, that it will be beneficial to patients." Likewise, Andrew Moss, an epidemiologist at the University of California, San Francisco warned, "There is a mounting groundswell for using surrogates . . . But I don't see how a decision can be made until more data are analyzed."

Despite the concerns expressed by some scientists, the Advisory Community unanimously approved the use of CD4 counts as a surrogate marker for examining the efficacy of AIDS treatments.

B. Accelerated Approval of ddI

The Advisory Committee's decision to use surrogate endpoints for purposes of analyzing AIDS drugs set the sage for approving ddI based upon CD4 counts, making it functionally the first drug to be granted accelerated approval (even though the regime was not formally implemented until the following year). At a press conference announcing ddI's approval, Dr. Fauci stated that he was convinced that CD4 counts could serve as a surrogate marker because a recent study that indicated that PWAs rarely died with CD4 counts above fifty, suggesting a correlation between CD4 counts and life expectancy. Therefore, the FDA approved ddI based upon data from a trial of patients who worsened while on AZT. While on ddI, these patients saw a ten percent improvement in CD4 counts.

Although the drug was granted full approval, Commissioner David Kessler warned that ddI would be withdrawn if Phase II results expected the following year did not demonstrate that the drug was effective. Indeed, that proof was forthcoming. In April 1992, Burroughs Wellcome

demonstrated that ddI reduced opportunistic infections in AIDS patients.

C. Reaction of Interest Groups to Approval of ddI

Many AIDS activists expressed delight with the FDA's decision to approve ddI using an accelerated approval-like procedure and then announcing the accelerated approval procedure itself. Martin Delaney declared that accelerated approval represented "the fruition of all that has gone into FDA reform for the last seven years." Moreover, he praised the FDA for granting patients increased autonomy to make their own risk-benefit tradeoffs, stating, "The issue is choice . . . And what is happening now that is so very important is the FDA recognizing that patients have the right and the intelligence to make their own treatment choices." AIDS activists also saw accelerated approval as a step that portended great hope for the future. In commending the FDA's decision, John S. James wrote, "This example removes hopeless delays which stood in the path of the new generations of AIDS drugs now being developed. It should speed not only the regulatory steps to approval, but the whole development process, as pharmaceutical companies realize that they now have a feasible path to market for potentially life-saving new drugs -- where they did not before."

The pharmaceutical industry likewise applauded the FDA's approval of ddI. David Cocchetto, Chair of the Fast Track Work Group of Pharmaceutical Research and Manufacturers of America (PhRMA) wrote that ddI's approval reflected, "an effort by the FDA to exercise broad flexibility in applying statutory standards to a drug for life-threatening diseases." He praised the FDA for "recognize[ing] that physicians, patients and FDA are willing to accept greater risks and uncertainties from products that treat life-threatening diseases compared with

products for less serious diseases."

Many cancer advocates, however, were upset that accelerated approval was only being applied to AIDS drugs. Beverly Zackarain, Director of CAN ACT, a cancer patients advocacy group fretted that, "There is no 'accelerated approval' for cancer drugs. There is no 'parallel track.' Those are AIDS specific. We're still on the outside looking in." Likewise, the Competitive Enterprise Institute, a free-market think tank in Washington DC, reported that an anonymous FDA official stated that the issue of accelerated approval is "very touchy," because "homosexuals are well organized and I think the FDA would be hesitant to take them on; the cancer and Alzheimer's patients are not as well organized."

Clinical researchers, however, were much less enthusiastic. One of the most outspoken opponents of accelerated approval was Deborah Cotton, an infectious disease specialist at the Harvard School of Public Health, and a dissenting member of the advisory panel on ddI. She warned, "I really think this is a mistake . . . I think that the precedent is troubling, and I think we will see companies coming forward and offering drugs with truncated data and studies, and they will cite this ddI approval as precedent for FDA licensure based on shabby data."

Another commentator expressed his view that the approval of ddI was a decision based upon politics, not sound scientific principles. According to Steven Epstein, "[T]he scientific basis was so contested, and the political pressures so extreme, that panelists sought to disentangle their separate roles as scientists and policy-makers—to make clear that as far as *they* were concerned, their vote was neither a scientific endorsement of ddI . . . . but rather a pragmatic policy decision. The panelists were going to allow activists to assume risks that patients themselves . . . .were demanding that they were entitled to assume."

D. Approval of ddC/AZT Combination

Shortly after issuing the accelerated approval guidelines, the FDA approved the use of a combination of AZT and ddC under the accelerated approval program. ddC appeared on the radar screen of PWAs after a report was released in June 1991 of a small Phase I study demonstrating that patients taking a combination of AZT and ddC did better than those just on AZT. The results were so promising that Margaret Fischel, a researcher at the University of Miami, stated that she felt "very comfortable" recommending the AZT/ddC combination to sick AIDS patients.

However, because the FDA had not yet approved ddC, illicit "buyers clubs" sprung up to provide PWAs with bootlegged versions of the drug made either overseas or in illegal domestic laboratories. Although these organizations were illegal, Commissioner Young in 1989 promised that he would not crack down on buyers clubs so long as the groups remained ""self-help, nonprofit clinics . . . as long as patients are not being harmed, clinics do not promote unproven products outside the clinic and the clinic does not serve as a subterfuge for a commercial enterprise." Nonetheless, in February 1992, the FDA began testing ddC from buyers clubs, and discovered that the pills ranged from being super-potent to worthless, and consequently the Agency urged the clubs to stop selling the pill. Simultaneously, the FDA encouraged Hoffman-LaRoche, manufacturer of ddC, to distribute the drug under the parallel track to the sickest AIDS patients, and it agreed to do so.

In April 1992, the FDA Advisory Committee recommended granting accelerated approval of ddC for use with AZT. They based their recommendations upon three small studies

demonstrating that this combination treatment raised CD4 counts. However, they also had to consider unfavorable data indicating that ddC alone was of no use AIDS patients, meaning that it could not help PWAs who were unable to tolerate AZT. It therefore voted against approving ddC for use as a monotherapy.

On June 22, 1992, Dr. Kessler announced that the FDA had granted accelerated approval for use of ddC in combination with AZT. He stated that the Agency was basing its approval on two small studies involving a total of less than one hundred patients; in both studies the patients' CD4 counts rose by 100 and that result was sustained for several months. The FDA demanded Phase IV studies demonstrating clinical benefit.

Like with the approval of ddI, approval of the ddC/AZT combination was met with mixed reaction. AIDS activists such as John S. James and Martin Delaney were pleased with the outcome. Moreover, many scientists, especially at the NIH, had become favorably disposed to accelerated approval. According to Robert Biggar of the NCI, if faced with the criticism that they were rashly relying on incomplete data, he would reply, "Well, we did the best that we could."

Deborah Cotton, however, was once again irate. She alleged that her panel was being forced to "pound the data into a scientific conclusion. Moreover, she stated her apprehension that accelerated approval would be counterproductive in the long run, stating, "We really have to ask whether relying on surrogate markers will hasten a cure or hinder it . . . .We're getting into a situation of such complexity that we may have a large number of agents being used and no way to distinguish among them . . . It's sad that we may have nothing to offer people in 1992 . . . It's sadder that in 2000 we may have nothing, too. In 2000 we'll look back and say, "If only we'd

done this in a more rational way."

E. Bad News from Berlin: ddC/AZT Combination

Unfortunately, unlike the favorable postmarketing data on ddI, the results of the Phase IV testing of ddC/AZT were disappointing. At the 9th International Conference on AIDS, held in Berlin in June 1993, Dr. Fischl released the results of a trial comparing the survival of AIDS patients who were taking just AZT, just ddC or a combination of ddC and AZT. The recipients of the combination therapy did see their CD4 level rise, but that was not correlated to any clinical improvement. The results thus indicated that not only did was AZT/ddC not clinically beneficial, but also that CD4 counts might not serve as a reliable surrogate endpoint.

Dr. Fischl attempted to highlight a silver lining in the study, namely that the combination therapy appeared to be more successful for patients who had CD4 cell counts ranging from 150 to 300. Although NIAID originally distributed a press release highlighting this conclusion, they later retracted it fearing they were being too positive about grim data. For this reason, David Barr of the Gay Men's Health Crisis sharply criticized Fischl stating, "The fact is that the combination doesn't work."

F. More Bad News from Berlin: The Concorde Study

In April 1993, Dr. Maxime Seigmann of Paris published a study in the journal *Lancet* in which the researchers compared early treatment with AZT to delaying treatment until the patients became symptomatic. Unlike American studies of AZT which were interrupted midway through because the drug raised CD4 levels as compared to placebos, the Seigmann study continued

(although patients being given the placebo were given the option of taking AZT). The study demonstrated that AZT neither prolongs life nor delays the onset of AIDS. However, the study did demonstrate that AZT raised CD4 counts throughout the study, further indication that CD4 counts might not be useful surrogate endpoints, at least in asymptomatic HIV patients.

When the results of the study were released in April, many American researchers were outraged, especially because the article in *Lancet* provided relatively little data. However, by the end of the Berlin conference, many had become convinced that the study in fact was valid. According to Dr. Fauci, "[T]he Concorde was an excellently performed study."

Even John S. James, the long-time proponent of CD4 counts as surrogate markers was resigned to the need for a new endpoint. Although he expressed suspicion about the methodology of the Concorde study, he nonetheless recognized that "if early treatment with AZT does work, it didn't work very well." However, James cautioned that the concept of surrogate endpoints should not be abandoned, because trials requiring clinical endpoints would fail since, "They would compete with each other for patients and resources . . . and when they were done, the drugs and treatment philosophies they started to test would be obsolete." Nonetheless, James did express hope that these unfortunate results would force the pharmaceutical companies to abandon "third rate" drugs such as AZT in search of medications that would be more effective.

G. Fallout from Berlin: Clash of the AIDS Activists over Protease Inhibitors

The gloomy presentations at the Berlin Conference sparked a new faction of AIDS activists who joined academic critics of the accelerated approval program and urged that it be slowed down so that more data on safety and effectiveness could be gathered. They also

demanded the use of a new surrogate marker in the place of CD4 counts. This effort was spearheaded by New York-based Treatment Action Group (TAG) an offshoot of ACT UP/New York.

The event that sparked TAG's mobilization was Hoffman LaRoche's announcement that it was preparing to file for accelerated approval for Saquinavir (Invirase), the first in a class of new drugs called protease inhibitors, based upon favorable results from a Phase II trial. Protease inhibitors are drugs that interfere with the HIV's protease enzyme, utilized by the virus to cleave polyproteins into the structural proteins and enzymes that the virus requires in order to function.

Shortly after Hoffman LaRoche's announcement, TAG wrote to Dr. Kessler urging the FDA not to grant accelerated approval for Saquinavir because the data submitted by the manufacturer was based upon a small study utilizing CD4 counts. TAG worried that granting approval based upon such flimsy data would create an "inappropriately low standard of evidential requirements" for this new class of drugs. TAG expressed particular concern because they felt Hoffman LaRoche had not complied with the Phase IV requirements for ddC. TAG demanded that the FDA take the time to plan "prospectively [for] a coherent, rapid and clinically useful development path for HIV protease inhibitors." The following month, TAG followed up this letter with a demand that for a full-scale trial of 18,000 people before approving Saquinavir, a study of unprecedented size for AIDS treatments. TAG first received prominence in an article in *Barron's* in August 1994 highlighting their cause.

Needless to say, this article prompted outraged amongst other AIDS activists, especially those from the West Coast. For example, John S. James affirmed his support for patient autonomy, and expressed fear that increasing the amount of time to approval would make AIDS

drugs less profitable and consequently less attractive for private sector research and development. He contended that longer trials would just waste time and be needlessly rigid. Delaney of Project Inform expressed his criticism more starkly, stating, "You can't stick a patient on Product X and just see how long they can stand on their feet. That is what they do in clinical trials now . . . But it definitely is not in the interest of patients, who are human beings fighting for their lives." Moreover, Project Inform circulated a petition supporting the current accelerated approval regime.

The climax of this debate occurred at the September 1994 FDA Advisory Committee Meeting on Accelerated Approval/Expanded access, which was held to discuss issues pertaining to the accelerated approval process for AIDS drugs, with a specific focus on protease inhibitors. The day before the conference began, Hoffman LaRoche announced that it would delay filing for accelerated approval until at least the middle of the following year because it wished to take more time to complete controlled trials. Dr. Kessler immediately noted that the cause of the delay was the manufacturer, not the FDA. TAG would later take credit for pushing the manufacturer to redesign its trials by expanding their size.

At the conference, Commissioner Kessler sought to find a middle ground, stating, "We've worked very hard over the last couple of years to really revamp the drug approval system for life-threatening and serious diseases . . . . On balance, accelerated approval has been a success. We are balancing the need to make drugs available to patients who need them most with getting good data." TAG reiterated their concerns that sufficient testing had not been done on the drugs currently on the market and that manufacturers were failing to perform required Phase IV studies. Contesting the conventional mantra of AIDS activists, Carlton Hogan stated, "I think

there is a very natural tendency to trust medicine in this age of antibiotics, and to believe a priori that taking 'something' is always better than taking 'nothing.' While comforting, this notion is also quite incorrect." Other AIDS activists maintained their support for the current accelerated approval program.

On December 7, 1995, the FDA ultimately granted accelerated approved Saquinavir for use in combination with any older nucleoside analogue (such as AZT, ddC, ddI). Prior to the approval, TAG issued a position paper in which it expressed disappointment with the results of the Saquinavir's effectiveness, especially because of its low level of bioavailability. TAG implied that the FDA was being manipulated by public relations efforts by drug manufacturers. John S. James expressed cautious optimism about the cocktail, although he too worried about the level of bioavailability.

However, upon approving the drug, the FDA noted that the manufacturer was formulating a new version with greater bioavailability, and that in the meanwhile Saquinavir was of some benefit to AIDS patients. Dr. Kessler noted that the NDA had been approved in ninety-seven days, a record for AIDS drugs. He reiterated support for the accelerated approval program stating, "When it comes to AIDS and other life-threatening diseases, we have learned to take greater risks in exchange for greater potential health benefits."

H. Post-Script: HAART—The Treatment Revolution

Between 1994 and 1996, three major discoveries were made which revolutionized both the way AIDS was understood and treated.

The first major breakthrough pertained to measuring the amount of virus in the body.

Towards the end 1994, scientists began developing an assay utilizing polymerase chain reaction (PCR) to determine the amount of active and dormant HIV stored in tissue, known as the "viral load." Previously, tests had only been able to measure the amount of active particles, which were thought only to comprise one percent of the virus in the body. Besides leading to a new understanding of how the HIV virus operates, as will be discussed below, scientists immediately recognized that viral load could function as a more accurate surrogate endpoint than CD4 counts. Because of this discovery, the FDA now generally accepts twenty-four weeks of suppressed viral load as an acceptable surrogate endpoint for accelerated approval; if the viral load is suppressed for forty-eight weeks, the drug can be granted regular approval.

The ability to assay for viral load enabled scientists to radically alter their understanding of the mechanics of HIV infection. Until publications in the journal *Nature* in January 1995 by Dr. David Ho and Dr. George M. Shaw, scientists believed that after initial infection, the HIV virus went dormant for a period of time before eventually overwhelming the immune system. However, these researchers observed that although an experimental protease inhibitor could decrease the amount of HIV to one percent of the original level, within two weeks every patient in the study had become resistant to the drug. They therefore calculated that between one hundred million and one billion viruses were being produced each day, and that the body was continually creating new T cells to replace those that were killed by the virus. Under this theory, the HIV virus and the immune system engage in continual battle until the point that the body is overwhelmed.

With this new understanding of how the virus' interaction with the human body, scientists made their most important development, the treatment scheme involving the protease cocktail.

Dr. Ho had observed that during the middle part of HIV's infection cycle, the viral load in the blood neared zero but then the virus ultimately proliferated rapidly. He surmised that during the dormancy phase, the immune system was destroying viral particles as quickly as they were being created, but residual stores of the virus remained in locations such as the lymph nodes where they could not be detected. Therefore, Dr. Ho deduced that the best way to stop HIV was not to wait until a patient became sick, but rather to stop HIV from reproducing altogether so that an individual's immune cells could regenerate without having to battle HIV.

Based on this model of HIV infection, Dr. Ho began experimenting with the idea of a cocktail, otherwise known as combination therapy. The problem with applying one treatment such as AZT or ddC had been that drug resistant strains could develop very quickly. Based on mathematical models, however, he concluded that applying a combination of three drugs would greatly reduce the odds that a given person might have viral particles with the appropriate three mutations enabling them to survive and proliferate. He therefore proposed developing a treatment cocktail, including at least one protease inhibitor in addition to older nucleoside inhibitors.

In March 1996, the FDA gave accelerated approval to two more protease inhibitors, Norvir (ritonavir) and Crixivan (indinavir), which it approved in two and one half months and one and one half months respectively. In March 1997, it granted accelerated approval to another protease inhibitor, Viracept (nefinavir) in slightly less than three months. These protease inhibitors became key components of cocktail therapies, which became known as "highly active antiretroviral therapy" (HAART).

For some patients, the results of HAART were dramatic. Measurable viral lode dropped

to virtually nothing, and patients who were near death returned to relatively normal health. Moreover, for at least some patients, the impact of HAART does not appear to diminish over time. According to Joep Lange, an investigator who studies AIDS drugs, "HAART is one of the great success stories of medicine." *Time Magazine* named Dr. Ho its "man of the year" for his efforts.

While HAART has granted a new lease on life for many AIDS patients, it is far from perfect and most certainly does not represent a cure. To begin with, the treatment regime has a variety of troublesome side-effects including an unusual distribution of fat called lipodystrophy, diabetes-like complications, brittle bones, and heart disease. Moreover, the HAART regimen is complicated for doctors to administer and requires patients to take a large number of pills. If the patient is not diligent about complying with his treatment regime, drug-resistant strains rapidly develop. Hopes that were initially raised that AIDS could be cured within just a few years have been dashed, and some scientists now fear that it is impossible to cure AIDS. That being said, scientists are still working on novel approaches to treating AIDS, including certain drugs that more easily can enter infected cells and others that attack stores of the virus such as the brain, male genitals and lymph nodes.

V. President Clinton's "Reinventing the Regulation of Cancer Drugs"

A. Political Pressure on the President to Apply Accelerated Approval to Cancer

Although the FDA indicated in 1992 that it would grant accelerated approval for cancer drugs, by 1996 it had only done so in one instance. By comparison, eleven AIDS drugs had been granted accelerated approval. Meanwhile, the FDA was under pressure from Congressional Republicans who were proposing a dramatic overhaul of the entire drug approval process. At many of these hearings, representatives of cancer patient groups pleaded for accelerated approval for oncology drugs.

One of the themes highlighted at these hearings was that the FDA was unfairly favoring AIDS patients at the expense of cancer patients. Eugene Schonfeld, Ph.D., President of the National Kidney Cancer Association, a management expert, and himself suffering from an advanced stage of cancer, testified that because the FDA approves AIDS drugs more rapidly than it does cancer drugs, it makes AIDS drugs relatively more profitable. Consequently, pharmaceutical companies were likely to shift resources towards AIDS drugs. Dr. Schonfeld testified that Hoffman La-Roche told him that they were shutting down trials for interleukin-2 (IL-2), a promising drug for kidney cancer, because they were shifting resources to AIDS research. Moreover, Dr. Schonfeld testified that Dr. Kessler told him that the reason AIDS drugs were being approved more quickly was that AIDS activists "are screaming louder" than advocates for patients of other diseases. Likewise, Ellen Stovall, Executive Director of the National Coalition For Cancer Survivorship lamented, "Perhaps the cancer community has been too reticent or willing to accept the agency's procedures," an obvious reference to AIDS activists who had put extreme pressure on the FDA for years.

A second theme highlighted at the hearings was that cancer patients were every bit as willing to take risks as were AIDS patients. Dr. Schonfeld related that in one conversation with Dr. Kessler, the Commissioner told him that that AIDS patients were willing to take risks whereas cancer patients would not. Dr. Schonfeld retorted, "[W]hy do so many cancer patients go to Mexico and the Bahamas for treatment?" Ellen Stovall similarly remarked that cancer patients were willing to risk taking chemotherapy despite its dreary side-effects, emphasizing that, "[O]ur very survival depends on accepting the risks of this nature."

B. Announcement of Plan to Apply Accelerated Approval to Cancer

On March 29, 1996, President Clinton announced that as part of Vice President Gore's National Performance Review, the Administration was implementing "Reinventing the Regulation of Cancer Drugs," designed to expedite development and review times for cancer products and to facilitate their distribution within the United States. This initiative included applying accelerated approval to cancer drugs.

In the document implementing the policy, the FDA explained that in the past, it had approved cancer therapies based upon clinical endpoints such as longer patient survival, decreased recurrence rate, longer disease-free intervals and/or improved quality of life. Although scientists had concurred that a complete disappearance of a tumor would be considered a valid surrogate endpoint, that was a result that was rarely achieved. The Agency had not previously consented to the use of surrogate endpoints because of a lack of scientific consensus on what constituted a valid surrogate.

However, the FDA explained that it was now willing to accept partial tumor shrinkage as

a surrogate endpoint for the purposes of accelerated approval, because objective tumor shrinkage appeared to correlate to longer survival or improved quality of life. Therefore, the FDA announced that tumor shrinkage could be used as a surrogate endpoint "for patients with refractory malignant diseases or for those who have no adequate alternative," so long as "the potential effectiveness of the treatment should outweigh its toxicities." Like with AIDS drugs, the Agency stated its expectation that postmarketing studies continue in order to verify clinical benefit.

At a press conference announcing the policy, Dr. Kessler reflected upon the lessons learned during the first five years of the accelerated approval regime. Commenting on the possibility that a drug given accelerated approval might prove ineffective or unsafe, he remarked, "We are taking some risks. We have to go into this with our eyes wide open. One day we're going to make a mistake, but I believe that's okay, especially when we're dealing with diseases for which there are not available therapies." Furthermore, he noted that accelerated approval had provided an incentive for pharmaceutical companies to manufacture AIDS drugs, and hoped that the same would prove true of cancer drugs.

C. Reaction to the Cancer Initiative

Needless to say, cancer patients groups expressed support for the plan, yet they urged that even more be done. For example, Kim Calder of Cancer Care testified that while her organization had participated in the drafting of the new program, she still worried that the initiative was insufficient because of the "wide discretion and inconsistency in the FDA's current regulatory agencies."

The pharmaceutical industry likewise expressed cautious optimism about the plan. Homer Pearce, an executive with Eli Lilly, explained that manufacturers previously had not sought accelerated approval for oncology drugs because the Agency had never provided guidance on how to proceed. Likewise, the Pharmaceutical Research and Manufacturers of America (PhRMA) issued a statement praising the move as "long overdue" yet noting like Ms. Calder that significant legislative changes were needed to further enhance the process of drug development. Furthermore, *Pharmaceutical Executive* observed that many of the FDA's reforms had come about as a means to deflect Congressional pressure for more dramatic overhaul, and expressed concern that if Congress stopped putting the Agency's feet to the fire, it would revert to its slower, more cautious ways.

Needless to say, the plan also had its critics. Dr. Sidney Wolfe of Public Citizen expressed concern that the FDA might in fact be setting itself up to "do[] more harm than good." He worried that the approving highly toxic drugs based on weaker demonstrations of efficacy would not be beneficial to patients. He also noted that although AIDS patients had originally clamored for faster FDA action, many (such as TAG) were now urging the Agency to act more cautiously. Although Dr. Wolfe at this point expressed his reservations in a relatively mild manner, his groups' opposition would grow in the years to come.

D. Post-Script: Dr. Jane Henney's Tenure at the FDA: A New Slowdown at the Agency?

Towards the end of the Clinton Administration, the FDA again came under criticism for slowing down the drug approval process. Specifically, Dr. Kessler's successor, Dr. Jane Henney (FDA Commissioner from 1998 through 2001), was condemned for decelerating drug approval

by creating new bureaucratic barriers designed to mitigate safety concerns. According to Pfizer's Chairman and CEO, Hank McKinnell, Dr. Henney should be blamed for "raising the regulatory hurdles quite significantly." He noted that in 1996, the FDA approved 56 new drugs, but in 2000 only 19 were approved. Mr. McKinnell quipped that the rejection rate did not rise because, "we got dumber," insinuating that the slowdown was caused by the Agency's bureaucracy.

The diminished rate of drug approval during these years was undoubtedly related to public criticism of the Agency. As has been previously discussed, the FDA has periodically faced a rash of criticism whenever a drug proved to have an unfortunate side effect, even in a small number of patients. This era proved not to be an exception.

In 1998, the FDA was subjected to significant condemnation because it gave "fast track approval" to Rezulin, a drug designed to treat diabetes that was allegedly responsible for the deaths of thirty-three individuals due to liver damage. The Agency was particularly criticized because it had removed the chief reviewer of the drug because he had been opposed to granting approval.

Around the same time, Public Citizen, released a report entitled "FDA Medical Officers Report Lower Standards, Permit Dangerous Drug Approvals." The report contained the results of surveys of the FDA's Medical Officers, in which many complained that drugs were being approved too quickly and that appropriate safety standards were not being upheld. In particular, the report expressed significant hostility to the accelerated approval process.

In response to the report by Public Citizen, the FDA in May 1999 released a lengthy report of its own entitled "Managing the Risks from Medical Product Use: Creating a Risk Management Framework." In the report, the Agency argued that since 1992 there had not been

any increase in the rate of drug withdrawal. After a lengthy exploration of risk-benefit assessments, report concluded with a meager suggestion that the FDA needed to convene a meeting "with stakeholders to discuss the current system of managing risks" so that they could consult "stakeholders" about different options for risk management. The report could be more appropriately characterized as bureaucratic banter than any kind of spirited defense of efforts to expedite delivery of drugs to critically ill patients.

This new slowdown was best typified by the story of UFT, a promising new cancer drug. In 1999, the ODAC unanimously recommended granting approval for the drug for use with leucovorin calcium tablets for the first line treatment of metastatic colorectal cancer. However, in March 2000, the FDA indicated that despite the fact the UFT was being marketed outside the United States, it would not approve the drug because it desired additional data unrelated to safety concerns. Therefore, the manufacturer, Bristol-Myers Squibb, withdrew the NDA. Congressman Thomas Bliley, chair of the House panel with jurisdiction over the FDA, expressed dismay at the Agency's decision. He characterized the failure to approve the drug as an example of, "regulatory overreach and detachment from clinical reality and patient needs." He worried that this decision portended an ominous trend, that the "FDA process' irrationality could over time seriously undermine U.S. drug development, thereby denying seriously ill Americans access to the newest therapies."

VI. An Intellectual Revolution? Mark McClellan's Tenure as FDA Chairman

A. Background: The Challenge Facing Dr. McClellan

By the time that Dr. McClellan arrived at the FDA, the results of the Agency's revived spirit of hyper-cautiousness were beginning to come to fruition. In the Center for Drug Evaluation's (CDER) 2002 Report to the Nation, Director Dr. Janet Woodcock noted that the number of approved molecular entities (NMEs) had dropped to the lowest level in a decade. The number of approved NMEs is significant because they reflect new drugs that have never previously been approved for marketing in the United States. Dr. Woodcock observed that the number of the FDA's priority drug reviews had also declined.

Many also feared that the accelerated approval program was slowing. According to Dr. Scott Gottleib, a health care expert at the American Enterprise Institute who later served as an advisor to Dr. McCllellan, warned that the FDA was "slowly slouching away" from the accelerated approval program.

B. McClellan's Efficient Risk Management Program

In order to reinvigorate the drug development process, Commissioner McClellan announced a new initiative entitled "Efficient Risk Management." Unlike the FDA's previous risk management report, this one had a significantly more free-market bent, aiming to "foster and encourage new product development by ensuring that [new drugs'] review and approval processes are efficient, transparent, and predictable," in order that new scientific discoveries be "turn[ed] into safe and effective medical products more quickly, and at lower cost."

One of the report's major aims was to counteract the trend of declining drug approvals.

The report noted that the decline occurred not because the Agency had begun increasingly to reject NDAs, but rather was because of a lower number of NDAs were reaching the FDA. Although the report observed that this trend could be explained in part because of a delay in translating new technological developments in fields such as genomics and proteomics into new drugs, the slowdown could also be explained by the high costs and uncertainties associated with new drug development. It cited estimates that a new drug can cost over $800 million to develop one new drug, and that reducing the time of the clinical phases by 41 percent could cut development costs by $200 million. The report therefore argued the best way to facilitate the transformation of cutting edge medical research into effective life saving drugs was to create a "simpler and more straightforward" system of drug development that reduced the time, cost and uncertainties inherent in the current system.

Commissioner McClellan offered several proposals to streamline the drug approval process under the rubric of "provid[ing] timely, high quality, cost-effective process for review of new technologies/premarket submissions." Specifically, he suggested reducing unnecessary product review cycles and developing specific agency guidance to assist industry where the development process is unclear.

C. Applying McClellan's Initiative to Accelerated Approval

During Dr. McClellan's short tenure at the Agency, he issued several proposals in the spirit of his Efficient Risk Management Program that were designed to significantly broaden the scope of the accelerated approval process. Although it highly uncertain if the FDA will follow his suggestions now that he is no longer with the Agency (and indeed the story of Marqibo,

discussed infra, indicates that it may not), the Commissioner's recommendations represent a paradigm for how the accelerated approval program could be enhanced and expanded.

Two of the most significant recommendations made by the Agency, one during McClellan's tenure and one shortly thereafter, pertained to interpreting the "meaningful therapeutic benefit to patients over existing treatments" requirement. In both cases, the FDA defined the clause broadly to encompass more drugs under the accelerated approval process. It is important to note that these recommendations were included in "Guidance for Industry" documents and are not binding, but rather reflect the FDA's general priorities.

The first issue pertained to defining "existing treatments." In a scenario where no drug had been given regular approval for treatment of a given condition, but one drug had already been granted accelerated approval and/or multiple drugs were in clinical trials, could the Agency grant accelerated approval for another drug designed to treat the same condition? The FDA responded in the affirmative because data from surrogate endpoints are by nature less certain. Consequently, the drug currently on the market could be withdrawn on an expedited basis should Phase IV testing fail. Therefore, the Agency defined "existing treatment" as one for which regular approval (based upon clinical benefit) had been granted.

The second question pertained to a related issue, namely if "existing treatments" included those not regulated by the FDA (such as surgical procedures) or off-label uses suggested in the medical literature but not approved by the FDA. In its "Available Therapy" Guidance, the Agency stated that existing treatments "should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions," the exception occurring when a therapy is "particularly well documented." The FDA stated two rationales for its

decision. First, by making it easier to achieve accelerated approval, it provided incentives for a manufacturer to complete expeditiously the studies required for regular approval. Manufacturers are incentivized to seek regular approval because attaining this status means that it is much more difficult for a competing drug to be granted accelerated approval for the same condition. Second, it provided an inducement for manufacturers to seek FDA approval for their off-label therapies.

Dr. McClellan also made a significant suggestion that the FDA grant accelerated approval for diabetes and obesity drugs by using lower blood sugar and weight loss as surrogate markers respectively. This proposal was remarkable for several reasons. First, unlike cancer and AIDS, diabetes and obesity are not immediately life-threatening. Second, considering the fallout over Rezulin and fen-phen, an anti-obesity drug, it was all the more remarkable that the Commissioner was suggesting to expand accelerated approval to medications designed to treat these diseases. McClellan defended his proposal stating, "We have an awful lot of premature death and huge morbidity associated with diabetes . . . While we've made some progress in treating obesity, this is one of the leading causes of death and disability in this country." Needless to say, the proposal elicited opposition from Peter Lurie of Public Citizen, who decried the suggestion as needlessly endangering public health in order to benefit pharmaceutical companies.

VII. Has the FDA Really Changed? The Story of Two Cutting Edge Cancer Drugs

A. Iressa (gefitinib)

1. Introduction

Iressa is a drug manufactured by AstraZeneca to treat non-small cell lung cancer (NSCLC). Lung cancer is estimated to have caused more than 160,000 deaths in the United States in 2004, of which are large percentage are from NSCLC. Smoking is one of the most common causes of NSCLC. If the cancer is caught in its early stages and is removed through surgery, cure rates exceed fifty percent. Unfortunately, if the cancer reaches stage three or worse, stage four, the likelihood of long-term survival is extremely poor. Besides surgery, the only treatment for NSCLC is chemotherapy, normally a platinum-based regimen. Unfortunately, chemotherapy frequently only helps patients in the short run, and has a litany of devastating side effects including anemia, hair loss, and severe fatigue. Therefore, the National Cancer Institute declares that "for most patients with NSCLC, current treatments do not cure cancer" and recommends that patients enroll in clinical studies.

Iressa is a member of a new generation of anti-cancer drugs. Traditional chemotherapy drugs attack all dividing cells, including non-cancerous ones, and consequently cause the horrendous side effects discussed above. Iressa is designed only to interfere with cancer's signaling apparatus. It does so in the following manner: Cells have epidermal growth factor receptors. When these receptors are stimulated by the binding of a particular molecule, the result is that their tyrosine kinase enzymes are triggered, leading to a cascade of events that de-activate programmed cell death (apoptosis). If there is a mutation resulting in this pathway being kept "on," cells become immortal and thus cancerous. Iressa is designed to bind to the receptor

molecule such that it is inhibited, thereby keeping the pathway "off." This "targeted" method should not have any adverse impact on normal cells.

2. ODAC Hearing: Iressa

CDER's Oncologic Drugs Advisory Committee (ODAC) met to consider accelerated approval of Iressa on September 24, 2002. The meeting began with emotional testimony by a series of women who had been treated with Iressa. They all described variants on the same story. All had been diagnosed with lung cancer, witnessed it spread, and been treated unsuccessfully with some combination of surgery and chemotherapy. They all related the horrors of the latter and described how the combination of treatments and their spreading cancer left them virtually unable to function, leaving some near death. However, after treatment with Iressa, their tumors receded and they were mostly asymptomatic.

AstraZeneca first presented the results of "Trial 39", a Phase II third-line monotherapy study that used tumor shrinkage as a surrogate endpoint. Trial 39 was a randomized, double blind study of 139 patients (slightly more of whom were males than females) who were either given 250 mg or 500 mg daily oral doses. The only eligible patients were those that previously had received two chemotherapy treatments (platinum-based and docetaxel) and had not responded to both or were unable to handle the toxicity. The result of the trial was a 10% FDA verified response rate and a total of forty percent had improvement in NSCLC-related symptoms. Amongst the objective responders, there were both men and women, and included patients that had been subjected to different numbers of prior regimens. Based on this data, the manufacturer applied for accelerated approval because there was no approved third-line treatment for patients

with NSCLC.

AstraZeneca conducted a second trial ("Trial 16") in Europe, Australia and Japan. This trial was also double blind and randomized, although unlike the other study, patients in this study were eligible even if they were less heavily pretreated with chemotherapy drugs, and generally patients were accepted even if they were more healthy. In this trial, the overall objective response rate was 19 percent.

Although a ten percent response is a relatively low level of effectiveness, AstraZeneca representatives explained that it was the largest response ever observed in such diseased patients. Several of the patients who were facing virtually imminent death lived for more than a year while being treated with Iressa. The manufacturer also expressed confidence in the drug because the results were verified in a Trial 16 that was based upon diverse nationalities.

AstraZeneca also presented the results of a first-line combination trial in which patients were given both chemotherapy and Iressa or were given chemotherapy and a placebo. Unfortunately in this trial, the patients that also received Iressa did not show any improvement over those who had just received chemotherapy. The manufacturer stated that although it was somewhat perplexed as to why this trial failed, they were quite certain that these results did not cast doubts on usefulness of the drug as a third-line monotherapy.

In analyzing the data presented by AstraZeneca, Dr. Grant Williams of the FDA noted that the panel would have to decide if a 10% tumor response rate was likely to predict clinical benefit. The reviewer expressed concern that the studies of Iressa as a monotherapy had neither included a placebo nor control arm. He worried about the value of the drug given its failure as a first line treatment with chemotherapy.

The first matter debated by ODAC was if they should consider data on symptom improvement; they decided by a vote of nine to five that they should not. Dr. Thomas Fleming, the biostatistician consultant on the panel, described symptom improvement data in an open-label trial as "treacherous" because of the possibility of a placebo effect. Furthermore, there might not be a relationship between survival and symptom improvement, since the patients experiencing symptom improvement could have been more healthy to begin with.

The panel then turned to the question of granting accelerated approval for the drug. During the discussion, panel members expressed a wide variety of perspectives. Many expressed significant concerns relating to the low level of efficacy. Dr. Silvana Martino noted that the drug "overwhelmingly . . . does not work," and observed that although it worked better in certain subgroups such as women and Japanese, it fared far worse with western males. Dr. Stephen L. George stated that although he had a feeling that "something is really going on," he was disturbed by the lack of control group, meaning that biases could have crept into the result. Dr. Claudette Varricchio, a consultant on the panel, worried that his colleagues might disregard efficacy data because of Iressa's favorable toxicity profile.

Dr. Richard Pazdur expressed some of the strongest criticism. Although he noted that the Committee had previously approved drugs with a ten percent response rate, he wondered if the panel would have been inclined to come to the same result without the symptom-improvement data. He then asked sarcastically, "And, then a question for you that we frequently get from sponsors is how low can you go?" Later in the meeting, Dr. Pazdur clarified that he was deeply troubled about the results of the first-line trial with chemotherapy and the manufacturer's inability to explain the results.

Despite these criticisms, members of the panel made favorable remarks about the drug. Dr. Donna Przepiorka, chair of the panel noted that ten percent response was very "substantial" for a third-line therapy and observed that she had never heard of a NSCLC patients whose tumor shrunk spontaneously; consequently the drug was undoubtedly of clinical benefit to at least some patients. She also dismissed the fears raised by the statisticians that the negative results presented in the first line trials had anything to do with the positive results in the third-line trial.

Replying to Dr. Pazdur's concerns, Dr. David Kelsen observed that although the ultimate clinical benefit of Iressa was still in doubt, data from the surrogate marker did demonstrate clinical activity, and the toxicity of Iressa was much lower than those of other drugs approved based upon 10% response rates. Dr. John Carpenter noted that he supported the drug because of a lack of alternative treatments, but urged further studies to elicit the best way to utilize it.

Ultimately, on the key question of whether or not the ten percent response rate was likely to predict clinical benefit, the panel voted in the affirmative by a count of 11-3. Thus, the panel recommended accelerated approval for Iressa.

3. FDA Grant of Accelerated Approval for Iressa

In May 2003 the FDA officially granted accelerated approval for Iressa as a third-line monotherapy treatment, meaning that doctors were supposed to prescribe it to patients who had seen their cancer spread after taking both platinum-based and docetaxel chemotherapies. As a condition of the accelerated approval, AstraZeneca agreed to conduct three clinical studies to evaluate the effectiveness of Iressa in different clinical settings.

Needless to say, cancer-patient and free-market advocates expressed delight with the

decision. Peggy McCarthy, founder of the Alliance for Lung Cancer Advocacy, Support and Education, praised the move because, "New treatments like Iressa are desperately needed to give these patients . . an alternative when chemotherapy fails." The *Wall Street Journal* wrote an editorial congratulating the FDA for "doing the right thing." The editorial reported that they had been told that Dr. Pazdur, a known skeptic of accelerated approval, had originally suggested that the manufacturer withdraw the accelerated approval application for Iressa and perform more trials, yet the manufacturer risked the wrath of the FDA by refusing this proposal. After noting that the panel was influenced by the moving testimony of patients who had improved on the drug, the editorial expressed hope that in the future the FDA would heed the advice of clinicians actually treating patients rather than bureaucrats who are more interested in statistics and avoiding condemnation.

Right before the FDA approved Iressa, Public Citizen sent the Agency a letter imploring them to not to do so. Public Citizen criticized Trial 39 because it tested a group of patients that had less severe forms of cancer, lacked a control group, and did not separate the effects of Iressa from other medications that the patients might have been taking. Furthermore, Public Citizen noted that in the trial of 23,500 patients in Japan, 473 developed interstitial lung disease, 173 died of it, and they hypothesized that more patients might also have suffered from the disease but their results had not been reported. Therefore, Sidney Wolfe warned that, "[T]he FDA would be putting patients in jeopardy by approving a drug that is already showing itself to be ineffective and dangerous." The FDA replied that it had spent three months reviewing the data from Japan and concluded that the rate of interstitial lung disease was much lower in the United States. Moreover, AstraZeneca's director of oncology explained that patients with advanced lung cancer

frequently suffer from interstitial lung disease regardless of what treatment regimen they received.

4. Negative Clinical Data and the Future of Iressa

This past December, AstraZeneca released the results of a large-scale postmarketing study of patients who had failed previous chemotherapy regimes, where one group was given Iressa and the other received a placebo. Unfortunately, the results indicated that the drug did not prolong survival. Although the results of the study again demonstrated an objective response rate that was similar to what was observed in previous trials, that did not correspond to prolonged survival. AstraZeneca's analysis of the data did reveal, however, that the drug appeared to provide clinical benefit for Asians and people who had never smoked. The manufacturer announced that it would leave Iressa on the market, although it sent letters to doctors informing them of the negative results and suggesting that they consider other treatment options if appropriate.

On March 4, 2005, the ODAC met to consider the results of the latest data. In advance of the meeting, Public Citizen delivered a letter to the FDA imploring them to remove Iressa from the market. Public Citizen leveled three charges against the drug. First, citing a FDA pharmacology reviewer, they claimed that contrary to the manufacturer's claims, the drug does not properly bind to the desired epidermal growth factor receptor. Second, citing this reviewer, they alleged that there was only a small differential separating a safe dose with one that was highly toxic. Third, they again raised concerns about patients on the drug contracting interstitial

lung disease. They also doubted AstraZeneca's claims that they could identify subgroups that were likely to benefit from the drug and noted that even those that responded to the drug often grew resistant over time. Instead, Public Citizen urged that patients suffering from advanced stages of NSCLC be provided with Tarceva, a drug that had recently been approved by the FDA.

In AstraZeneca's briefing document to the FDA, they expressed surprise that the trial had not yielded data demonstrating prolonged survival. However, they urged the Agency not to withdraw the drug from the market, noting that Iressa is undoubtedly pharmacologically active and does appear to be effective in some subgroups. They stated that as part of a complete analysis of this trial that they hoped to provide by May or June of 2005, they would also undertake genetic research to determine if certain mutations rendered patients more or less sensitive to the drug.

At the ODAC meeting, the panel considered AstraZeneca's data but did not reach any final conclusions. Although troubled by the results, panel members appeared hesitant to remove the drug from the market. According panel member Dr. Maha H.A. Hussain, "Ethically, it's going to be very hard to say to a patient who's on it and is responding, or is likely to respond when there is nothing else, that you can't get it . . . On the other hand, I think it's also unethical to keep it available for people who we know are not likely to benefit." However, the whole approval process for Iressa came under criticism. According to Dr. Otis W. Brawley of the ODAC, "The development of this drug has been mishandled . . . It's been mishandled by AstraZeneca. It's been mishandled by this committee . . . We still haven't figured out how it should be used." One option considered by the panel involved re-labeling Iressa, indicating that it would only be used after patients have been supplied with Tarceva because the latter has been

demonstrated to prolong survival. However, an unnamed industry lawyer quoted by *FDA Week* suggested that the Agency might require a "black box" label restricting Iressa's use to population subgroups most likely to benefit from the drug.

B. Marqibo (vincristine sulfate liposomes injection)

1. Introduction

Marqibo is Inex Pharmaceutical's proprietary delivery system for the off-patent, anti-cancer drug vincristine, and is designed to treat non-Hodgkins lymphoma (NHL). Lymphomas are cancers that originate in the lymphatic tissues, which are located throughout the body. NHL has a much greater likelihood of proliferating than does Hodgkins lymphoma and consequently is more dangerous. It is estimated that 54,370 cases were diagnosed in 2004 and there were 19,410 deaths. NHL can be divided into two groups: aggressive and indolent. Patients with indolent NHL fare much better than those with the aggressive form of the disease. The median survival for the indolent form is ten years; if caught in the early stages, it can be treated with radiation. However, there is usually no way to cure indolent NHL at an advanced stage.

For aggressive NHL, the picture is more bleak. The first line therapy for treating this disease is a combination of rituxiamb and CHOP ((Cytoxan (cyclophosphamide), Adiamycin (hyroxy doxorubicin), Vincristine (oncovin), Prednisone). This treatment cures approximately half the patients with aggressive NHL. In the event of relapse, patients under the age of sixty-five are treated with high-dose chemotherapy and autologous stem-cell transplants. If a patient is unable to receive a transplant or the transplant fails, the outlook is dismal; only ten percent of

patients are cured and the median life-span is only six months. Additionally, after each relapse, the likelihood of survival further diminishes. There are no proven therapies for patients who reach this stage. Between 10,000 to 15,000 patients are in need of third line therapy or later.

Marqibo functions by concentrating the level of vincristine at locus of the cancer and increasing the duration that the drug remains in the bloodstream. Vincristine operates by inhibiting the cell's ability to divide at a very particular point in the cell cycle. The problem is that at a given time, only five percent of a person's cells are at the appropriate stage. Therefore, the longer vincristine is in the bloodstream, the greater the number of cells at that will reach the point in their lifecycle where they will be susceptible to the drug. Marqibo consists of vincristine packed into special liposomes which are delivered intravenously into the bloodstream. Normally, these liposomes will remain stable in the bloodstream. However, when the blood approaches the area where the lymphomas are located, the neovasculature (blood vessels supporting the cancer) are porous, and the liposomes are sized appropriately to slip into the interstitial space where the cancerous cells reside.

2. ODAC Hearing: Marqibo

In order to determine the effectiveness of Marqibo, the manufacturer performed two Phase II studies. The Phase IIa study was performed at M.D. Anderson Medical Center, and included both leukemia and lymphoma patients, including 92 who had relapsed NHL. The Phase IIb study was an international multi-center study involving 119 patients. Two-thirds of the patients were partially resistant to their previous treatment, including half that were truly refractory, meaning that they completely failed to respond to their previous treatment. Thus a

large percentage of the patients had diseases that were very difficult to treat. These Phase II trials utilized Marqibo as a monotherapy and used objective response as the primary surrogate endpoint.

Dr. Fernando Cabanillas, a lymphoma expert at M.D. Anderson, testified that the drug had an overall response rate of 25 percent, including a 46 percent response rate for patients treated upon their second relapse. Based on these results, Marqibo was the "most single active agent" for NHL that he had tested since the 1970s.

Some of the patients were also analyzed for clinical benefit. Of the 43 cases analyzed, 26 experienced some improvement in their symptoms. Six of the patients in the study became sufficiently healthy to become eligible for stem cell transplants. Several patients testified that they had experienced several relapses after chemotherapy and that Marqibo had enabled them to be cancer free for a significant period of time and/or had enabled them to receive bone-marrow transplants. Although all the patients complained of neuropathy, one commented that the benefits of the drug far outweighed the side effects.

Marqibo also proved to be relatively safe. An Inex representative testified that the safety profile for Marqibo is no different than that of conventional vincristine treatments. Fourteen percent of patients withdrew from the study because of toxicity, mostly because of neuropathy, which frequently manifested itself with numbness of the hands. That number, however, can only be understood in the context of the fact that eighty-six percent of the patients in the study had already been treated with two treatment regimens that contained neurotoxic agents. Moreover, the toxicity associated with Marqibo developed in a "gradual and predictable" way, so the doctor and patient could accordingly develop a treatment plan.

After the presentation by the manufacturer, Dr. Maitreyee Hazarika, a medical officer at the FDA, presented the Agency's analysis of the studies performed by Inex. He first noted that according to the Agency's calculations, the overall response rate was only 21 percent. After raising multiple technical concerns regarding the trials' protocols, he warned, "The study conduct raises doubt regarding the method of assessment of response. The duration was short and not adequately evaluated. The use of the supportive study is questionable for support. There is no confirmatory trial underway."

After the presentations, ODAC began debating the question of whether or not there were other drugs "available" for the treatment of NHL. As has been previously noted, the FDA only grants accelerated approval if there are no other treatments available. In explaining the criteria for accelerated approval, Dr. Pazdur detailed cases where there literally were no approved treatments for treating the disease in question; he cited Iressa as one example. The difficulty posed by Marqibo was that there were off-label treatments for NHL described in the medical literature. In explaining the issue facing the committee, Dr. Pazdur explained, "[W]hat we are looking for . . . is [if] there is enough evidence that you have from the literature that you feel that there is *compelling* evidence that there is available therapy that would warrant a randomized study." Dr. Pazdur went on to explain that "compelling" is a "very vague word, it is like beauty, it is like sexy, it's in the eyes of the beholder."

Dr. Chesson mentioned several off-label NHL treatments that have response rates of around thirty percent, lasting three months. He also noted that radioimmunotheapeutics have been used to treat third-line patients with NHL, and they have an average response rate of forty-three percent; however their use is limited because of marrow suppression. Likewise, one of the

consultants for the panel, Dr. Wyndam Wilson, stated that Marqibo is "very much in the middle of the pack" for other agents, and he therefore desired to subject Marqibo to a randomized comparison trial with etoposide if given the opportunity. Thereupon, the committee agreed unanimously that other treatments for NHL were available, although two members expressed some hesitation concerning their votes.

The next issue, whether the Committee would only accept complete responses, or also partial responses as surrogate endpoints, served as a springboard for the most explosive rhetoric of the day, as Drs. Pazdur and Martino began bashing the entire accelerated approval process. Dr. Pazdur began by picking up where he left off during the Iressa hearing, contrasting a mere demonstration of pharmacological activity with, "saying . . . this drug is ready for prime time here for general use with all of the ramifications that has associated with it." Thereupon, Dr. Martino concurred that the entire problem with the accelerated approval process was that manufacturers were always asking, "[W]hat is the least amount that you can show me, to which I will then give you a reward for that?" Instead, she demanded that manufacturers search for "grander" objectives. At that point, Dr. Pazdur interjected, "The only thing I have to say, Silvana, is go, girl, go." Dr. Pazdur then reiterated his objection to manufacturers always expressing the mantra, "How low can you go?" Furthermore, he emphasized that the purpose of the regime was not "accelerated drug company profits" and likewise "wasn't a license to do less, less, less, to a point now that we may be getting companies coming in, well, what is the lowest. It shouldn't be what is the lowest." Dr. Martino concurred, "[I]f we keep rewarding such behavior, we will see more and more of it."

Replying to the tirades by Drs. Pazdur and Martino, Dr. Ronald Bukowski restated the

traditional justification for accelerated approval:

> I mean it may not be necessarily the issue of how low can you go, but is there anything else available in the area that can be utilized, and I think that is very, very important, because clearly, there are many situations where there are unmet needs, where new agents may well have a very minimal or modest response rate or modest activity, but still these may be useful, and I think the issue is, is getting those agents out to patients in a very timely basis, with subsequently then doing the appropriate studies to demonstrate the clinical benefit associated with the agent.

In response, Dr. Pazdur stated that while he agreed in theory with this justification, accelerated approval should only be granted "in a real clinical situation . . . []not a contrived situation." He cited the example of a drug manufacturer developing a medication to treat leukemia patients on a respirator, but the only reason that the patients were on the respirator to begin with was because they were being treated with a drug for which the same manufacturer was also seeking approval. However, Dr. Pazdur never elaborated why the Marqibo studies were "contrived."

After this discussion, the Committee considered several more issues, and ultimately voted unanimously against recommending accelerated approval for Marqibo. Not surprisingly, the next month, the FDA officially informed Inex that it was denying accelerated approval. Consequently, the manufacturer announced that it would seek regular approval once it had data from a randomized Phase III study. It also stated that it would be forced to reduce its workforce from 165 to 62 employees as part of a significant cost-cutting effort.

The ODAC came under fierce criticism for failing to recommend Marqibo for accelerated approval. In a *Wall Street Journal* editorial entitled, "Pazdur's Revenge," the editors decried the current environment in which trial lawyers were threatening to ravage the pharmaceutical industry because of Vioxx and Celebrex, Senator Charles Grasserly was badgering the FDA to increase regulation of new drugs, and at the Agency, "some bureaucrats are using the current

political climate as cover to turn back what little progress has been made on drug approval times." The editors were referencing Dr. Pazdur, whom they accused of "offering a twisted interpretation of the McClellan guidelines (Available Therapy Guidelines) that basically entirely reversed their original intent." Furthermore, they warned that "The Pazdur interpretation of the rule would effectively kill the accelerated approval process, since there are off-label therapies for just about everything." Finally, the editorial condemned "the apparent relish with which some of the panelists dismissed the efforts of Marqibo's makers . . . and fired back at the patient activists who've been uppity enough to suggest faster access to developmental drugs," making reference to Dr. Pazdur's "Go, girl, go" comment.

Dr. Scott Gottleib of AEI, who had served as a senior policy advisor to Dr. McClellan (speaking only for himself) also condemned the ODAC's decision, calling it "a perversion of original intent, and a potentially dangerous step backwards when it comes to making drugs available for unmet needs." He rebutted the ODAC's argument that accelerated approval was unnecessary because there were other drugs on the market, noting that, "The real value of having a drug like Marqibo on the market is just that it has a different safety profile and a different side effect profile . . . By not having a therapeutic variety, it would deny patients the ability to make that choice." Furthermore, he suggested that the FDA was being hypocritical by touting off-label NHL therapies, while at the same time it was extremely unlikely that the Agency would consider the same data sufficient for placing NHL on these drugs' labels.

VIII. Perspectives on the Accelerated Approval Process

A. Academic Criticism

As indicated by some of the harsh rhetoric at the Iressa and Marqibo hearings, many clinical academicians have significant misgivings about the accelerated approval process. These concerns can be grouped into four categories: (1) the poor efficacy of approved drugs (2) the insufficiency of Phase II data used as the basis for accelerated approval (3) the questionable value of many of the surrogate endpoints that frequently have been utilized and (4) the failure of manufacturers to identify in which population subgroups targeted cancer drugs are likely to be effective.

1. Efficacy Concerns

Dr. Pazdur's complaints about the pharmaceutical industry's alleged mantra, "How low can you go?" reflects his concern that the ODAC has been pressured into granting accelerated approval to drugs of insufficient efficacy. These views have been presented in the course of the debate over Iressa and Marqibo, supra.

2. Questionable Value of Phase II Data

A frequent theme in the oncology literature over the last several years has been that the FDA has been granting accelerated approval based upon data that has either been faulty or incomplete. Clinical academics have been particularly troubled that applications for accelerated approval have not been supported by "gold standard" studies, namely Phase III, randomized, double blind controlled trials with a substantial number of patients. Rather, accelerated approval

has frequently been based upon open relatively small, Phase II, open label studies.

Of particular concern is that open label Phase II trials carry a high risk of selection bias. In an editorial entitled *Selection Bias, Phase II Trials, and the FDA Accelerated Approval Process*, Dr. Stephen L. George warned that "patients enrolled on clinical trials often bear little resemblance to the larger population of patients to which we wish to generalize the results because of the complicated processes by which patients are identified and recruited for clinical trials." He supported this point by referencing a study of cancer patients demonstrating that patients who traveled longer distances to clinical trials were likely to live longer. He noted that the study had controlled for all observable demographic, medical or socioeconomic factors that are known to alter clinical outcomes, yet they could not account for this travel bias and surmised that there must be an unknown variable influencing the results. This is worrisome because by definition is it difficult to know how an unknown variable might affect the outcome. To the extent that the data are randomized to a control, the influence of any unknown variable can be minimized.

Dr. George argued that the influence of such biases are particularly magnified in small, non-randomized trials, exactly the type that are frequently submitted by applicants for accelerated approval. He criticized Iressa's original Phase II trials submitted by AstraZeneca for accelerated approval because of the combination of low efficacy rate and small number of patients enrolled. He deemed the study especially problematic because it never analyzed the characteristics of the patients participating in the trial, such as how far they were traveling to be treated. He concluded by arguing that accelerated approval should not be granted solely on the basis of Phase II data.

Other scientists have warned that another problem with Phase II data being submitted for accelerated approval is that it is often based upon patients with highly refractory tumors. This poses several difficulties. First, patients with refractory tumors frequently have already been subjected to prior treatment regimes, complicating the effort to isolate the effect of the new drug. Consequently, it is all the more difficult to predict if the effect on the surrogate endpoint will in fact reflect an improved clinical outcome. Second, the impact of pharmaceuticals on refractory patients may not be relevant to patients with non-refractory tumors. Third, trials of patients with refractory tumors may actually sometimes understate the benefit of certain treatments because while the response rates may in fact be low (i.e. the tumors may not shrink), the drug may in fact be delaying the tumor from growing larger, which may lead to extended survival.

Another problem with approving drugs based upon Phase II studies is that is impossible to know if they are in fact safe. In an editorial in the *Journal of Clinical Oncology* entitled "Hurry Up and Wait: Is Accelerated Approval of New Cancer Drugs in the Best Interests of Cancer Patients?" the writers explained that in the trials of three cancer drugs, accelerated approval was granted on the basis of a mere 305, 570, and 1435 patients (increased to 875, 955, and 2,045 at the time of regular approval) and that in the case of one of the drugs, three years after being given regular approval, two large trials had to be stopped because of a previously unrecognized toxicity and risk of early death. They warned that although common side effects are usually known at the accelerated approval stage, until the drug is used on a large number of patients (either in clinical practice or large-scale trials) it is often difficult to discern unusual side effects, rare drug interactions and toxicities that only occur in certain population sub-groups.

Determining safety profiles of drugs administered to patients with refractory tumors

presents an additional challenge. In the case of single-armed trials of highly pre-treated patients with refractory tumors (like the Iressa third-line trials) it is difficult to determine if an observed toxicity is the result of the current medication or some combination of the tumor and prior treatments.

Some have alleged that granting accelerated approval based upon Phase II trials could actually harm patients in the long run because it diminishes the incentive of manufacturers to complete required marketing (Phase IV) trials that are far better indicators of both safety and clinical effectiveness. Critics have noted that out of the twenty-two drugs that have received accelerated approval, only six have completed the Phase IV trials necessary for receive regular approval. They claim there are several reasons that pharmaceutical companies have been dilatory in fulfilling their obligations. From the patient's perspective, there is little incentive to enroll or stay in the trial once the drug is on the market, because participating in a clinical trail entails needlessly risking receiving a placebo instead of being treated with a cutting-edge drug. Furthermore, once the drug has been granted accelerated approval, it will usually available on the market and reimbursed by insurance, so patients no longer need to participate in clinical trials to receive the drug and/or have its cost reimbursed. From the vantage point of the pharmaceutical companies, once their drug has been granted accelerated approval, confirmatory studies have relatively little upside because all they can do is to replicate claims that the drug is effective. The downside, however, could be quite severe should the study demonstrate that the drug is ineffective and/or dangerous.

Despite the claims of these critics, there is an alternative explanation for why confirmatory trials have not yet been completed. The fact that Phase IV trials are unfinished

does not mean that the manufacturers will fail to do fulfill their commitments. Indeed, as demonstrated in the Appendix, in addition to the six drugs already granted regular approval, the results of two confirmatory trials have already been submitted to the FDA, seven are ongoing (proceeding according to schedule), three are pending (the study has not begun but the enrollment date has not yet passed), and only one is delayed. Thus, fifteen out of twenty two trials are either complete or are proceeding on schedule, and the FDA has not claimed that any of the studies have failed. There does not appear to be a crisis of failure to complete Phase IV trials; rather these studies are long and complex just require sufficient time to complete.

Several recent articles in medical journals have proposed an alternative paradigm for granting accelerated approval that should surmount many of the difficulties that clinical academics believe are posed by relying upon Phase II data. The proposed strategy mimics the procedure for granting accelerated approval in AIDS drugs. Under this protocol, the entire approval process is based upon one large randomized trial. Accelerated approval can be granted after twenty-four weeks if there has been a favorable impact upon a surrogate marker. Regular approval is granted if the same patients demonstrate clinical improvement after forty-eight weeks. This model has once been used for cancer. Oxaliplatin, an element of a second-line therapy for advanced colorectal cancer, was granted an approval based on an interim analysis of a randomized trial where the surrogate endpoint was an objective response rate and time-to-tumor progression. The plan was to grant regular approval at the end of the trial assuming that the duration of survival had in fact increased.

Granting accelerated approval based upon an interim analysis of a large study is supposed to provide several advantages. First, since accelerated approval is granted half way through the

trial, the manufacturer has less incentive to quit because the study is already substantially underway. Patients are likewise not as likely to drop out just because the drug has been approved. This is also advantageous because the patient population that served as the basis for the accelerated approval will also serve as the basis for the regular approval. Second, such a study will minimize the difficulty in ascertaining safety because the trial will be of a longer duration and can be measured against a control.

Third, a randomized study permits a meaningful analysis of time-to-event surrogate endpoints such as time-to-progression (TTP). TTP measures the amount of time that it takes for tumors to spread; delaying TTP is significant, because when tumors spread, patients almost inevitably die. TTP is especially valuable for the purposes of analyzing so-called cytostatic agents that do not shrink tumors, but rather prevent them from growing any further. This surrogate endpoint can only be analyzed in the context of a randomized trial with a control, because historical estimates of TTP are considered unreliable.

Fourth, randomized studies can facilitate an investigation of drug combinations. Thus, a study could examine the difference in results between standard therapy and the standard therapy plus the new drug in question. This presents a significant opportunity, because unlike single armed studies that are generally only performed on patients with highly refractory tumors where no other therapy is available, an investigation of a combination of drugs can be performed on less-refractory patients, which is advantageous for the reasons described above.

3. The Challenges of Using Valid Surrogate Endpoints

Underlying many academics' demands for more randomized controlled trials is the fear

that many surrogate endpoints are in fact ineffective at predicting clinical outcomes, a claim made in a strongly-worded article by Dr. Thomas Fleming, a biostatistician and member of the ODAC. Dr. Fleming begins by arguing that "a correlate does not a surrogate make," meaning that even though a particular surrogate marker is correlated to a clinical endpoint, if the surrogate marker is not part of the pathway guiding disease progression, then altering it likely will not have any clinical impact. For example, it is well known that HIV-infected women who have low CD4 counts and high viral loads are more likely to infect their children. Therefore, one might predict that both CD4 counts and viral loads could serve as valid surrogate endpoints. However, scientists have determined that that viral loads are part of the causal pathway leading to HIV transmission whereas CD4 counts appear to be a mere side effect. Thus, a drug like interleukin-2, which merely increases CD4 levels and does not alter viral loads, is not going to be effective. For this reason, Dr. Fleming argues that in order properly to validate a surrogate endpoint, one should ideally have a "comprehensive understanding of the causal pathways of the disease process and of the intervention's unintended and intended mechanism of action." He argues that this constitutes, "an extremely complicated challenge" which frequently requires a meta-analysis of many randomized controlled trials.

Dr. Fleming develops a hierarchy of means of measuring outcomes. Level 1 represents a true clinical efficacy measure, such as reduced risk of heart attack or stroke, or improved quality of life. Level two is a validated surrogate endpoint, for which the outcome is not itself a clinical benefit but is directly related to one. For example, providing a HIV-infected mother with a short term regimen to lower viral load will not improve the health of the mother, but there is a high likelihood that it will reduce the risk of transmission. Level 3 is "reasonably likely to predict

clinical benefit," the standard for accelerated approval. Dr. Fleming argues that there are four criteria for properly meeting Level 3: (1) evidence that altering the surrogate marker will impact the pathway through which the disease proceeds, (2) there is significant data indicating that the drug does not have a harmful impact which might not be reflected by the surrogate endpoint, (3) statistical analyses suggest that the outcome on the clinical endpoint is consistent with what is predicted by the impact on the surrogate endpoint, and (4) the effect on the surrogate endpoint is sufficiently strong based on the first three criteria that it is reasonably likely to predict meaningful clinical benefit. Level 4 occurs when data indicates that the drug is biologically active and hence altering a marker, but there is not evidence that the marker is causally related to the progress of the disease (for example, the CD4 example cited above).

Dr. Fleming laments the fact that accelerated approval process has frequently been granted based upon Level 4 markers because such drugs frequently have no clinical benefit but may have toxicities that not have been detected by the time of accelerated approval. He argues that it is not in patients' best interests to have more drugs on the market without reliable data on the drugs' effectiveness, especially if the drugs are costly and/or toxic. Therefore, he urges that Congress mandate that accelerated approval be granted only when the criteria for Level 3 endpoints are met and when clinical trials are in place to provide "statistically compelling evidence, within a well-defined rapid time frame."

4. Targeted Drugs and Failure to Identify Appropriate Subgroups

In a recent article, Drs. Thomas G. Roberts and Bruce A. Chabner highlighted a special challenge posed to the accelerated approval regime by cutting edge oncology drugs that

specifically target cancer cells. Such drugs may not be effective in the overall population, but rather may only impact certain population subgroups whose tumors have particular molecular characteristics. For example, studies of Iressa indicate that certain mutations on cell receptors make tumors uniquely sensitive to the drug, meaning that patients with such mutations are most likely to respond. However, the FDA has never required manufacturers to identify the subpopulation in which a targeted drug is most likely to work.

Information on which subpopulations are likely to respond to a targeted drug is critically important for patients. Individuals who know that they are unlikely to respond to a drug can avoid taking it, which saves them unnecessary costs, spares them unpleasant side effects, and provides them with valuable time to pursue treatments that are more likely to be successful.

Unfortunately, pharmaceutical manufacturers currently have little incentive to determine which subgroups are most responsive to their drugs for several reasons. First, since the FDA has granted accelerated approval to drugs with as little as ten to fifteen percent effectiveness, manufacturers have little incentive to identify subgroups in order to secure approval. Second, so long as the drug in question is the only one that can treat the disease (a common occurrence), the manufacturer has no need to identify a population subgroup as a means of demonstrating the drug's efficacy. Third, at least in the short run, identifying population subgroups could actually diminish revenue because desperate patients will take any drug on the market, even if it has a low level of efficacy. Should a large percentage of patients realize that they were not in the appropriate subgroup (a likely corollary of low efficacy), they would cease taking the drug. Finally, identifying the characteristics of a drug that make it suitable for certain subgroups can be extremely complex, expensive and time consuming.

In order to rectify these problems, the authors recommend mandating a special form of accelerated approval for targeted cancer drugs they call "selective approval." Under this regime, accelerated approval would be granted to targeted drugs only if the manufacturer had at least begun (although not necessarily completed) studies to identify subgroups of patients that were likely to respond to the drug. These studies would use tools such as genomics profiling, gene sequencing, proteomics and molecular imaging. Moreover, the manufacturer would commit to allocating a small percentage of sales (the authors propose 5 percent) to continuing this research either until such time as the drug received regular approval or the appropriate subgroups were identified.

Selective approval could provide several benefits. First, as discussed above, the costs associated with treating patients unlikely to respond to the drugs could be avoided. Second, such research could provide scientists with unanticipated information on what diseases their drug might treat. For example, a drug designed to treat one type of cancer could also impact another form of cancer with a completely different clinical manifestation but resulting from the same underlying mutation.

B. A Reply from Industry: Clinical Approval as an Art, not a Science

In response to the criticisms raised by ODAC panelists about the accelerated approval process, Dr. Antonio J. Grillo-Lopez, the industry representative to the panel (non-voting), presented a radically different perspective on the drug approval process that challenges many of the views elaborated above. Unlike his colleagues who have displayed a quasi-religious devotion to statistical data, Dr. Grillo-Lopez contends that experimental data are frequently

flawed and that subsequent statistical analyses are far less meaningful than their protagonists maintain. The major problem is that "[c]linical data are never 100% accurate, relevant or specific." One of the significant flaws in statistics is that no matter how many controls researchers use, human beings are heterogeneous and researchers still are not even able to measure certain critical variables. For example, scientists are unable effectively to measure certain immune system responses and bone marrow reserves, data which could be critical for cancer trials. A second difficulty is that variables relating to subjective sensations are virtually impossible to quantify because they are idiosyncratic. Dr. Grillo-Lopez mocked the increasingly complex forms of analysis demanded by statisticians on the grounds that not only do they fail to provide meaningful guidance on clinical outcomes, but that they obfuscate the only question that researchers can answer with any certainty, which is whether or not the drug is active. Hence Dr. Grillo-Lopez's mantra is that statistics should be used as "a tool . . . to serve me rather than being enslaved by statistics."

Rather than viewing drug approval as a process of sifting through statistical data to determine the "right" answer, Dr. Grillo-Lopez believes that the oncology drug approval process is an art, not a science (a view completely antithetical to that of his colleagues on the ODAC). He stated, "Clinical medicine . . . is an art that requires intimate knowledge of the patient . . . .An art that requires treating the patient as a human being, as much as, or even more than, the indispensable knowledge of physiology, pathology and posology. It quires joining and fitting together all of these considerations in order to heal." Therefore, he argued that the drug approval process should reflect the clinician's "skill and experience as an artist as well as his scientific and technical knowledge."

In the place of lengthy, complex clinical trials that inhibit the delivery of new drugs to cancer patients, Dr. Grillo-Lopez offers a new paradigm of a two-stage process for developing and deploying oncology drugs: drug development, a process which FDA is required to regulate by law, and treatment development, which should be left to the "oncology community" (academic institutions, cancer centers, other cooperative groups) and not the Agency.

Dr. Grillo-Lopez argues that for oncology drug development, the FDA should aggressively implement the accelerated approval process, granting applications based upon Phase II data. The Agency's goal should be to make the trials as "efficient and straightforward as possible," so that the process can be, "collapsed to the shortest possible timeframe." The advantage of streamlined trials are two-fold. First, such studies should immediately highlight agents that are in fact ineffective (approximately five out of six drugs tested in clinical trials fail), leaving manufacturers to allocate their resources more efficiently. Second, this process would enable patients to have speedier access to drugs that that appear to work.

Dr. Grillo-Lopez defines cancer treatment as the process of determining the optimal way to combine already approved drugs into effective anti-cancer treatment cocktails. Figuring out how to best utilize a new anti-cancer drug in combination with other agents is a complex process that requires large Phase III studies and sometimes can take decades to perfect. However, so long as the drug development process proceeds rapidly and is disconnected from the cancer treatment process (meaning that it is liberated from the heavy hand of FDA regulators), cancer patients can have rapid access to the newest and most promising drugs. Even if a new drug displays a relatively poor level of efficacy and definitive combination therapy studies are

ongoing, many patients may still stand to benefit because skilled practitioners utilizing their knowledge and instincts developed over years of practice may be able to develop combinations that enhance the drug's level of effectiveness.

Dr. Grillo-Lopez suggests implementing this scheme by creating three categories of oncology drugs. The first is drugs that appear to function better, even as a monotherapy, than other agents currently on the market. These are the drugs that should be granted accelerated approval based upon relatively small Phase II studies. He notes that although that there is an outside chance that the drug may later prove to be toxic or more ineffective than previously thought, if that situation occurs, then the drug can be withdrawn or it will simply stop being prescribed. Moreover, this small risk is far outweighed by the immediate benefit to patients whose cancer has been previously untreatable and are otherwise likely to die.

The second category involves drugs that appear to be effective as a monotherapy, but at a lesser rate than other drugs on the market. Drugs in this category, however, may still be promising if it appears that their efficacy can be enhanced because of synergies with other agents. Currently, the FDA will only approve such drugs based upon complicated Phase III trials that demonstrates that the new drugs are superior or at least non-inferior to the standard treatment regimen. Dr. Grillo-Lopez contends that this approach is misguided, and that the Agency should approve such drugs based upon a Phase II study and leave it to the oncology community to determine how to most effectively utilize them. Presumably his rationale is that for patients who are currently resistant or allergic to the standard treatment, this new therapy, even if possibly not the most effective, may be their only hope. Moreover, it is always possible that researches may be able to develop a combination therapy that is in fact superior to the

standard treatment.

In the third category are drugs which are ineffective as a monotherapy, but may have synergistic effects when combined with other drugs. According to Dr. Grillo-Lopez, this is the only category of drugs that must be approved based upon randomized, controlled Phase III studies. Accelerated approval presumably would be relatively useless in this context because giving drugs to patients that have not yet demonstrated any efficacy would mean needlessly exposing them to possible toxicities.

Thus, in Dr. Grillo-Lopez model, drugs in two out of the three categories should be approved rapidly. This provides several significant advantages. Most importantly, gravely ill patients will have access to the newest drugs at the earliest possible date. Moreover, if the drug trials are shorter, development costs are likely to shrink and consequently the drug should be cheaper.

C. A Patient/Outsider's Perspective: Why aren't there Real Victories in the War on Cancer?"

In a piece entitled "Why We're Losing the War on Cancer [And How to Win it]," Clinton Leaf of *Fortune* (himself a cancer survivor) contends that the United States has failed miserably in fighting cancer and that significant changes are required for the oncology drug approval process. Although much of the article deals with issues of how cancer drugs are researched go beyond the scope of this paper, his criticism of the way the FDA approves cancer drugs and his suggestions as to how to improve the process are relevant to the debate over accelerated approval. While Mr. Leaf shares many of the concerns of the academics cited above, he, like Dr. Grillo-Lopez, is a strong proponent of combating cancer with treatment cocktails.

Mr. Leaf begins the article by relating the dreary statistic that the percentage of Americans currently dying of cancer is the same as it was in 1970 and as it was in 1950. Moreover, even the claim by researchers that patients are living longer than ever with cancer is somewhat misleading, because that extended longevity is usually only measured in months. Only in a small subset of diseases (including Hodgkin's disease, certain leukemias, thyroid and testicular cancer and juvenile cancers) have seen actual cures developed.

Mr. Leaf believes that one of the major flaws in the oncology drug approval process is reliance upon tumor regression as a surrogate endpoint. He contends that tumor regression is a poor predictor of ultimate clinical outcome because by the time that malignant solid tumors are diagnosed, they are likely to metastasize and spread throughout the body, ultimately killing the patient. Therefore, unless the doctor is successful in killing every last cancer cell, merely shrinking the tumor is useless. Unlike stopping metastasis, which is extremely difficult to do, it is much easier for manufacturers to demonstrate tumor shrinkage, especially in refractory patients. Thus, Mr. Leaf is sympathetic to Dr. Pazdur's complaint that oncology drugs are being submitted to the FDA with unacceptably low levels of efficacy.

Mr. Leaf also argues that the clinical trial process itself is deeply flawed. First, trials are so burdensome that a recent study indicated that 97% of patients refuse to participate. Second, clinical trials have become so expensive that drug companies are only willing to fund them if they know the drug will receive FDA approval. Third, as mentioned above, because it is easier to demonstrate tumor shrinkage on the sickest patients, manufacturers have an incentive to run trials only on those who likely cannot be cured even if the drug might prove more successful on relatively healthy patients. Fourth, the many trials ultimately demonstrate only that one drug

does a slightly better job than another of treating a given cancer, a result that is not particularly useful for patients.

The reason that cancer has proven so difficult to cure is that cancer cells can mutate easily, thereby skirting treatment. Mr. Leaf argues that the best approach for fighting cancer is to utilize a method similar to that designed to treat AIDS, namely developing treatment cocktails. However, like Dr. Grillo-Lopez, Mr. Leaf agrees that the FDA approval process is poorly suited for evaluating cocktail treatments. The difficulty is that, if multiple drugs are tested together, it is very difficult to determine which drugs are actually working and/or which drugs might be responsible for a given side effect. The complications are even greater when products from multiple companies are involved. For example, Dr. Genie Kleinerman of M.D. Anderson related a story of repeated attempts to encourage cooperation amongst manufacturers on a trial of combination therapies for treatment of a particular form of juvenile cancer. One trial took so long that the biotechnology company went out of business in the interim. In a second, the lawyers from both companies fought so long that they ceased cooperating. In a third trial, the combination actually proved successful, but the trial broke down because both sides squabbled over who had rights to the combination.

Mr. Leaf contends that, for cocktail treatments to be successful, several major changes in the drug approval process are going to have to be made. The first is legal and regulatory reform to make combination trials more feasible. According to Homer Pearce of Eli Lilly, "I think everyone believes that at the end of the day, cancer is going to be treated with multiple targeted agents . . . it's a future that we have to embrace—though it will definitely require different modes of cooperation." The second is that the NCI should fund cocktail trials. Although the data from

such a trial could not be used to secure approval of the individual drugs, favorable results would entitle the manufacturers of those drugs to some kind of expedited review. Finally, a revised regulatory regime should permit administering these combination therapies in the earliest stages of the disease to patients who are the most likely candidates to actually be cured.

IX. Analysis: Reinvigorating the Accelerated Approval Process

A. The Perils of Excess Caution

The accelerated approval regime has witnessed a long string of successes since its inception in 1992 including HAART, the treatment cocktail that has transformed AIDS from an impending death sentence to at least a quasi-manageable disease, and more than twenty oncology drugs, some of which hold the promise to revolutionize cancer treatment. Yet, since the early days complaints by TAG and academics such as Deborah Cotton, to the increasingly fierce rhetoric recently leveled by Dr. Pazdur ("how low can you go?"), his colleagues in the ODAC and those writing in the medical journals demanding a higher threshold for granting accelerated approval, the process has been subjected to the same pressure faced by the FDA since the 1960s to place caution ahead of getting new drugs to market.

While excess caution might be appropriate for so-called lifestyle drugs or even drugs in a category for which there are already multiple successful treatments on the market (especially if the disease is not life threatening), adding new barriers to the accelerated approval process is grossly unfair to patients facing a terminal disease for which there is no known cure. To put it differently, Drs. Pazdur and Martino do not suffer adverse consequences awaiting a drug that has a high rate of efficacy in treating aggressive third-line NHL for which every other treatment has failed and the patient is too sick to receive a bone marrow transplant. For a practitioner facing a dying patient in his office, Marqibo, while admittedly imperfect, may represent the only hope. A drug whose efficacy is uncertain is far preferable to the otherwise virtual certainty of death.

B. The Price of Uncertainty in the Drug Approval Process

Besides being unfair to patients in the short run by keeping potentially life-saving drugs off the market, the demands of Dr. Pazdur and his colleagues ignore the economic realities of the pharmaceutical industry. As noted in Dr. McClellan's "Efficient Risk Management" report, one of the major challenges faced by the pharmaceutical industry is the significant uncertainty in the drug development process. Dr. McClellan's observation is undoubtedly rooted in the FDA's long history of being highly sensitive to complaints that too many unsafe drugs are on the market, and on the rare occasions when the Agency has agreed to speed the drug approval process after being inundated by political pressure, it has rapidly backtracked to its default overcaution mode with little warning.

The FDA's highly cautious attitude began with the public outcry over Thalidomide and the resulting legislation that "fixed" a problem that did not even exist in the United States, as the Agency had sufficient power under existing law to prevent the importation of this dangerous drug. Worse yet, by mandating premarket approval and adding an efficacy requirement, the legislation created a whole series of bureaucratic hurdles which, combined with the subsequent two decades of congressional criticism, led to a virtual halt to the drug approval process. Although years of complaint by economists that these delays were causing far more harm to the public than any offsetting good went unheeded, the FDA's inertia was only overcome by dramatic rallies, stunts, and protests by AIDS activists, culminating in the accelerated approval process. If Dr. Schonfeld was characterizing Dr. Kessler correctly, AIDS activists were only able to accomplish their goals because they were able to "scream[] louder" than anyone else.

At the same time that AIDS activists were able finally to spur the FDA into action, cancer activists making the exact same demands (albeit without the same political fervor) were ignored until 1996 when they were able to team up with congressional Republicans seeking to completely overhaul the Agency. Only then did the FDA agree to consider granting accelerated approval to cancer drugs, in large part to mitigate the political pressure for more dramatic action. Unfortunately, as *Pharmaceutical Executive* rightly predicted, only a few years later the Agency began backsliding, undoubtedly influenced by "scandals" such as Rezulin. By 2002, evidence was developing that fewer new drugs were being approved and that the accelerated approval process in particular was slowing.

Although Dr. McClellan's leadership may temporarily have spurred the FDA to reinvigorate the accelerated approval process, if there was any change in Agency mindset, the experience with Marqibo indicates that it has rapidly dissipated. As was discussed above, one of the purposes of Agency Guidance was to increase transparency between regulator and industry so that uncertainty could be diminished. However, as noted in the *Wall Street Journal*'s "Pazdur's Revenge" editorial, the ODAC may have accomplished exactly the opposite result by flaunting the Available Therapy Guidance that the FDA had only promulgated several months beforehand.

As previously discussed, Dr. Pazdur defines therapies as being currently available when there are indications "from the literature that you feel that there is *compelling* evidence that there is available therapy that would warrant a randomized study." However, this is a departure from the Guidance, which defines availability as, "therapy that is specified in the approved labeling of regulated products," with only "rare" exceptions, occurring only when a therapy is "particularly

well documented." In addition to a dearth of evidence that any of the other off-label NHL treatments were based upon sufficiently convincing data to qualify as being "particularly well documented," competing treatments may result in far worse side effects. For example, radioimmunotherapeutics cause marrow suppression, which for many patients is likely to be far worse than neuropathy.

The heated rhetoric by Drs. Pazdur and Martino, in combination with literature published by their colleagues criticizing the accelerated approval process, can only lead the pharmaceutical industry to wonder if the FDA has lost its commitment to the accelerated approval process. This is all the more true after the recent spate of congressional and consumer-advocate criticism over Vioxx and Celebrex, and now Tysabri. Consequently, a drug industry executive pondering risking hundreds of millions of dollars on new cutting edge research may be deterred from making the investment out of fear that the FDA will soon significantly raise the standard required to achieve accelerated approval. The only certainty that can come from the Agency continuing to reject drugs such as Marqibo, which while not a blockbuster represents at least modest improvements for an otherwise untreatable disease, is that heightened uncertainty is likely to shrink the number of candidates for accelerated approval in the future.

C. Economic Burden of Enhancing Data Requirements

Added uncertainty is not the only problem facing the pharmaceutical industry. If Dr. Pazdur and his colleagues get their way, the accelerated approval process will become significantly more burdensome. This is especially true should Phase II open label trials be rejected in favor of either more random controlled trials and/or trials designed along the lines of

the AIDS protocol.

Although there is nothing wrong with the AIDS model in theory (and indeed some well-financed drug companies may wish to use it either because they desire more comprehensive data and/or they seek a marketing advantage by having successfully completed Phase III studies sooner), the problem is that in many instances it may represent an immense economic burden, especially for fledgling drug companies. As discussed in Dr. McClellan's report, the cost of a successful drug is more than $800 million, an amount strongly correlated to the duration of drug trials. Indeed, according to a recent report by Bain & Co., this cost has now soared to $1.7 billion. To the extent that a manufacturer can shorten the drug approval process by marketing their product after receiving accelerated approval based upon a relatively cheap, open label Phase II trial, companies will have the resources to fund more complex Phase IV confirmatory trials. This in turn means that drugs designed to treat life-threatening diseases will become more profitable, attracting more investment to the field. However, to the extent that manufacturers are required to achieve up-front enrollment of a larger number of patients and to undertake the added expenses required for a double-blind trial, many of the financial incentives provided by accelerated approval may rapidly disappear. This difficulty is further compounded by the reluctance of cancer patients to participate in random controlled trials out of fear of receiving placebos.

Likewise, Dr. Fleming's proposal to grant accelerated approval only when his stringent Level 3 requirements are met and trials are in place to gather "statistically compelling evidence" could eviscerate many of the benefits provided by accelerated approval. Although he couches his argument in theoretical terms, his condemnation of the current regime for approving

pharmacologically effective drugs without adequate toxicity data and his strong rhetoric at the ODAC meeting indicate his significant distrust for the current regime. As Dr. Grillo-Lopez has observed, biostatisticians have developed an increasing appetite for large sets of data, and Dr. Fleming's article undoubtedly confirms that assertion.

The "selective approval" plan by Drs. Roberts and Chabner for targeted cancer drugs would also be extremely costly and likely technically unfeasible to carry out on a wide-spread basis, at least in the short term. Undoubtedly determining which population subgroups are sensitive to a targeted cancer drug would be beneficial to the public, yet for the reasons that the authors themselves identify, performing this type of analysis is extremely expensive and not in the financial interest of the pharmaceutical industry. Merely mandating that pharmaceutical companies commence this research and set aside five percent of sales towards continuing it without providing any countervailing benefits would make targeted cancer drugs relatively costly and could actually serve as a disincentive to their creation. Considering that targeted cancer drugs have the potential to be far more effective than chemotherapy yet without the horrific side effects, this result would be very unfortunate.

Although adding any type of additional requirements for the accelerated approval process would pose a challenge even to large drug manufacturers, it would likely prove especially devastating for small pharmaceutical and biotechnology companies. According to Dr. Gillo-Lopez, there are currently more than four hundred cancer drugs being researched by small companies with scarce resources, and they cannot afford large clinical trials. Inex Pharmaceuticals is a case in point. As previously noted, after being denied accelerated approval, they were forced to lay off approximately two-thirds of their workforce in order to afford the

Phase III testing now mandated by the FDA. It is entirely likely that, for a small company struggling to survive, while receiving accelerated approval under the current mechanism would enable it to sell drugs that could finance the company's future, mandating large up-front expenditures might force the company over the edge.

D. The Ultimate Outcome: From Approving Drugs to Treating (and Hopefully Curing) Patients

Ironically, the accelerated approval process may do best what its critics decry most, namely create an incentive to get biologically active anti-cancer drugs with relatively benign toxicity profiles onto the market as rapidly as possible. To patients otherwise facing death, new drugs provide at least a glimmer of hope. In the best of cases, accelerated approval has been responsible for nearly miraculous cures, such as Gleevec, a drug designed to treat chronic myeloid leukemia (CML). (It was granted accelerated approval at a record rate of less than three months.) The challenge comes from drugs of the type criticized by Dr. Pazdur for having low efficacy rates. Currently, even if these drugs do not work in the overall population, they are of tremendous benefit to the subgroups that do respond. The question is if there is a way to make such drugs useful for a broader segment of patients with a given disease.

In the view of Dr. Pazdur and his colleagues, it is preferable to avoid this dilemma entirely by rejecting drugs such as Marqibo and only granting accelerated approval to drugs for which manufacturers can provide overwhelming amounts of data detailing efficacy. Implicit in this argument is that it is better for cancer patients to have fewer drugs that are demonstrated beyond the cavil to provide clinical benefit rather than have more drugs on the market whose efficacy is less certain. However, this approach has several flaws. As discussed above, it is

unfair to patients facing death to deny them any meaningful option that might save their life. But more fundamentally, it assumes that there is no reason to approve a drug which is biologically active yet whose clinical impact remains unproven. This assumption is highly debatable because, as Dr. Grillo-Lopez has pointed out, a drug may be useful to a practitioner even if it does not appear as such to the biostatistician, whose models can be far less accurate than they are willing to admit.

A better approach involves seeking innovative ways to utilize the drugs that already have already been approved (and similar drugs that should be approved in the future) in ways that enhance their clinical effectiveness. According to both Dr. Grillo-Lopez and Mr. Leaf, this goal can best be accomplished with treatment cocktails designed to launch multiple "assaults" on a given cancer. Treatment by cocktail should proceed along two tiers, namely in the doctor's office and in large scale studies, and as Dr. Grillo-Lopez suggests, should be relatively free of FDA regulation.

As Dr. Grillo-Lopez has explained, one of the most important advantages of having a multitude of new anti-cancer drugs on the market is that it gives skilled practitioners an opportunity to adjust dosage levels of one drug or a combination of drugs in order to determine how best to treat a patient. In determining which drug(s) are most likely to be effective in treating the patient, complicated demonstrations of efficacy by biostatisticians are often of far less use than the practitioners own experience and that of colleagues in identifying what mode of treatment is most likely to be successful. For a patient battling an "uncurable" cancer, their doctor's off-label experimentation with biologically active cutting edge drugs (especially those with relatively favorable toxicity profiles) is far preferable to awaiting drugs with efficacy levels

high enough to satisfy Dr. Pazdur, especially because the drug dreamed of by Dr. Pazdur may never exist (at least in the foreseeable future).

Although practitioner experimentation may represent the best hope in the short run, in the long term it is vitally important to develop clinical data on treatment cocktails. However, as noted by Mr. Leaf, that approach is beset with several difficulties. First, as he observed, if the drugs come from more than one manufacturer, then a whole series of legal and financial issues that arise if two competitors are required to coordinate the trial. Second, in order to receive official labeling by the FDA, the sponsors of the trial will most likely have to proceed through randomized clinical trials, which might involve comparing the cocktail treatment to the current best standard of care. This is particularly problematic if patients perceive the current standard to be inadequate and refuse to enter the trial out of fear of receiving a placebo (especially if the new drug is on the market). Third, if the drugs comprising the combination have already been approved by the FDA, the pharmaceutical companies may lack an economic incentive to finance more trials that would likely be very expensive.

One intriguing possibility for investigating combination therapies mirrors a proposal made by John S. James in 1996 at a time when AIDS treatment cocktails were first developing. He suggested replacing the current clinical trial structure with a competition whereby each manufacturer would be urged to submit the strongest treatment cocktail they could devise, including drugs from their competitors if necessary. One of the main advantages of such a trial structure is that patients would not have to fear receiving the outdated treatment, since each combination would represent the most cutting edge approach that companies could provide. If manufacturers could be encouraged to participate in such competitions, it might spur the type of

creative thinking in combining cancer drugs that Mr. Leaf has described that is so desperately needed.

The challenge, however, is making trials of combination therapies economically feasible for drug manufacturers. There are several possibilities for accomplishing this goal. First, to the extent that one (or possibly) more of the drugs has only received accelerated approval, the FDA could accept data of the drug's clinical effectiveness from results in combination therapy trial as sufficient to grant regular approval. Second, the federal government, whether in the form of the NCI or other Institutes, could fund (or at least partially fund) such studies, and the participatory federal agencies could mandate inter-company cooperation as a prerequisite for joining the trials. Finally, Congress might provide large financial rewards for a company or coalition of manufacturers that were able to develop a cocktail for which the FDA could certify as providing a substantially enhanced longevity (possibly over several years) for a list of currently untreatable forms of cancer.

In addition to developing combination therapies, special attention should also be paid to Drs. Roberts and Chabner's suggestion that research be performed to identify subgroups that are most likely candidates to be effected by a targeted cancer drug. As noted before, there are two major problems. One is that it is still scientifically very difficult to accomplish. The second is that mandating the identification of subgroups comes at substantial cost to the pharmaceutical manufacturer with relatively little corresponding benefit. There are several ways to make identifying population subgroups economically viable. One option is simply to have the federal government fund such studies. However, in this era of tight federal budgets, this may not be possible. An alternative approach would utilize patent law as a possible incentive. Congress

might provide that if a manufacturer that creates a targeted cancer drug and successfully identifies the subgroups that are most likely to be sensitive to it, the drug's patent would be extended by a given amount of time. Such economic incentives would hopefully provide sufficient reward to manufacturers to encourage them to push the cutting edge of scientific research to determine ways of identifying receptive subgroups. If such a program could be implemented successfully, the public benefits of having targeted cancer drugs combined with the knowledge of how best to utilize them, in addition to the savings from not administering medications to patients unlikely to be responsive to them, would far outweigh the added drug costs from a lengthened patent term or other form of public expenditure.

E. Conclusion

Since its inception, the accelerated approval program has simultaneously fulfilled two important goals, namely ensuring that patients with life-threatening diseases receive access to the newest medications as soon as possible, while providing pharmaceutical companies with a strong economic incentive to develop such drugs. So long as scientists have not yet discovered cures for countless life-threatening diseases, the FDA should overcome the temptation to make the perfect the enemy of the good by creating new hurdles in the drug approval process designed to approve only drugs meeting the high efficacy threshold demanded by biostatisticians. Instead, they should continue granting accelerated approval for drugs so long as they are safe and meet minimal efficacy standards, ensuring that practitioners and clinicians will have as many cutting-edge options at their disposal as is scientifically feasible. This in turn should enable them to utilize their ingenuity, intuition and creativity to devise new treatment options that will hopefully make inroads on diseases such as cancer and AIDS that have ravaged countless millions of

Americans.

Appendix: Cancer Drugs that Have Received Accelerated Approval

Product	Indication	Approved	Manufacturer	*Status of Phase IV Trials
Zinecard (dextazoxane)	Prevent cardiomyopathy associated with doxorubicin	5/26/1995	Pharmacia & Upjohn (now part of Pfizer)	Fulfilled
Doxil (doxorubicin liposome)	AIDS-related Kaposi's sarcoma	11/17/1995	Sequus (now part of Johnson & Johnson)	Submitted
Ethyol (amifostine)	Reduce platinum toxicity in non-small cell lung cancer	3/15/1996	US Bioscience (now part of MedImmune)	Ongoing
Taxotere (docetaxel)	Metastatic breast cancer	5/14/1996	Aventis (now Sanofi-Aventis)	Fulfilled
Camptosar (irinotecan)	Metastatic colorectal carcinoma	6/14/1996	Pharmacia & Upjohn (now part of Pfizer)	Fulfilled
Xeloda (capecitabine)	Metastatic breast cancer	4/30/1998	Roche	Fulfilled

Ontak (denileukin diftitox)	Persistent or recurrent cutaneous cell lymphoma	2/5/1999	Seragen	Ongoing
DepoCyt (cytarabine liposomal)	Lymphomatous meningitis	4/1/1999	SkyePharma	Delayed
Doxil (doxorubicin liposomal)	Metastatic ovarian cancer	6/28/1999	Sequus (now part of Johnson & Johnson)	Unknown
Temodar (temozolomide)	Refractory anaplastic astrocytoma	8/11/1999	Schering-Plough	Ongoing
Celebrex (celecoxib)	Familial adenomatous polyposis	12/23/1999	Searle (now part of Pfizer)	Ongoing
Mylotarg (gemtuzumab ozogamicin)	Acute myeloid leukemia (AML)	5/17/2000	Wyeth-Ayerst (now Wyeth)	Ongoing

Gleevec (imatinib)	Chronic myelogenous leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of IFN-alpha therapy	5/10/2001	Novartis	Fulfilled
Campath (alemtuzumab)	Chronic lymphocytic leukemia (CLL)	5/7/2001	Millennium, Ilex	Ongoing
Gleevec (imatinib)	Gastrointestinal stromal tumors (GIST)	2/1/2002	Novartis	Submitted
Zevalin (ibritumomab tiuxetan)	Non-Hodgkins Lymphoma	2/19/2002	Idec (now Biogen Idec)	One commitment delayed, another pending
Eloxatin (oxaliplatin)	Metastatic colorectal carcinoma	8/9/2002	Sanofi-Synthelabo (now Sanofi-Aventis)	Fulfilled
Arimidex (anastrozole)	Adjuvant treatment for hormone receptor-positive early breast cancer	9/5/2002	AstraZeneca	Pending
Gleevec (imatinib)	Ph+ CML	12/20/2002	Novartis	Pending
Bexxar (tositumomab)	NHL	6/27/2003	Corixa	Ongoing
Iressa (gefitinib)	NSCLC	5/3/2003	AstraZeneca	Pending

*Definitions:

Pending: The study has not begun (i.e., no subjects have been enrolled), but the projected date for patient accrual (enrollment) has not passed. If patient accrual has started, but is not complete, and the projected date for completion has passed, the study is categorized as *delayed*.

Ongoing: The study is proceeding according to, or is ahead of, the original schedule. A study is considered ongoing until a final study report is submitted to FDA, as long as the activities are proceeding according to the original schedule.

Delayed: The study is proceeding, but it is behind the original or final study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to FDA. While the original schedule — not a revised schedule — serves as the basis for defining a study as delayed, each phase of the study is considered in its own right. If the applicant has one delayed phase, but makes up for it in the next phase and gets back on schedule, the *delayed* status will no longer apply.

Terminated: The applicant ended the study before completion or does not intend to complete the study as it was originally designed, and the applicant has not yet submitted a final study report to FDA.

Submitted: The applicant has completed or terminated the study and has submitted a final study report to FDA, but the Agency has not yet advised the applicant whether the study commitment has been fulfilled.

Fulfilled: The applicant has submitted the final study report for the commitment, and upon review of the final study report, FDA is satisfied that the applicant has met the terms of the commitment.