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Approval of New Drugs by the U.S. Food and Drug Administration  
Problems with the Process and Access to Unapproved Drugs

by

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Thesis

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## ABSTRACT

Today, the vast majority of drugs available for patient use have gone through a rigorous system of human clinical trials supervised by the Food and Drug Administration (FDA), to ensure the drugs are safe and efficacious. There are now citizen advocacy groups that seek use of drugs not yet approved by the FDA, to be administered to terminally ill patients who have exhausted all other available means of therapy. The FDA has programs for terminal patients, under the supervision of their physicians, to use unapproved drugs; however, the advocacy groups seek access to drugs in much earlier phases than is now allowed, raising serious safety concerns for patients. Use of drugs outside of the clinical trials system undermines the integrity of the FDA's drug development process by slowing enrollment, which in turn slows approval and timely access of safe and efficacious drugs to all of society.

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## Introduction

The U.S. Food and Drug Administration (FDA) walks a fine line between ensuring drug safety and approving effective therapies in a timely manner. The agency comes under fire both for moving too slowly in approving drugs and for allowing access to potentially dangerous substances. The pivotal question is, How are patients best served? Is it better to have a drug approval system that facilitates access to promising drugs, even if it means sacrificing opportunities to collect more rigorous information that could guide clinical decision-making down the road? Or is it better to enact measures that restrict access to experimental drugs in order to preserve the ability of the clinical trial process to develop rigorous, long-term medical information? The aim of this paper is to review the history and current status of the FDA drug-approval process and to examine problems with and ways to improve the process, with specific emphasis on new cancer treatments.

The FDA drug approval system has many deficiencies. The current system has served well for the last 50 years, but the demands of 21st century medicine are beginning to disclose problems, through dwindling approvals of new drugs, incremental improvements in cancer treatments, and patient dissatisfaction. Patient advocacy groups, such as the Abigail Alliance, and some U.S. senators have sued the FDA in court and introduced bills in Congress

that would allow the use of experimental drugs not yet approved by the FDA for marketing or compassionate use (Harris, 2007). Now more than ever, the clinical trials process needs to be strengthened with new innovations and increased enrollment. Because of the potential effect on the safety of patients, and the integrity and value of the FDA clinical trial system of making drugs safe for society as a whole, non-approved experimental drugs should not be available for use outside the FDA clinical trial system.

#### History of the FDA

The FDA is a regulatory, scientific, and public health agency that oversees most food products, human and animal drugs, biological therapeutic agents, medical devices, cosmetics, animal feeds, and radiation-emitting products for consumer use (Kurian, 1998). The agency also advances public health by accelerating innovations that make medicines safer, more effective, and more affordable, while supplying accurate science-based information the public needs to use these medications effectively (U.S. Food and Drug Administration, 2006).

The modern clinical trial process was founded in 1938, in the wake of a therapeutic disaster (Kurian, 1998). In 1937, a drug company combined sulfanilamide with diethylene glycol, a highly toxic form of antifreeze. The drug was used to treat streptococcal infections. This

concoction killed more than 100 persons. Congress reacted swiftly by passing a bill called the Food Drug and Cosmetic Act (FD&C Act) of 1938 (Milestones in U.S.FDA Food and Drug Law History, 1999). This act states that no person “shall introduce or deliver for introduction into interstate commerce any new drug unless” (Milestones in U.S.FDA Food and Drug Law History 1999) an approval of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is effective with respect to that drug (*History of the FDA*, 2006). An NDA is the vehicle by which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during animal studies and human clinical trials of an Investigational New Drug become part of the NDA. Through these trials, the sponsor must provide substantial evidence that the drug will have the effect it is represented to have (*History of the FDA*, 2006). An AND, a shortened version, may be submitted instead of an NDA for approval of a new formulation of an existing drug or investigational drugs that are similar to already approved drugs (*Title 21 Code of Federal Regulations 314.93*, n.d.).

The Kefauver-Harris Amendment to the FD&C Act was passed in 1962 as a result of thousands of birth defects in Western Europe, due to the use of thalidomide (*Drugs and Food Under the 1938 ACT and Its Amendments*, n.d.). The FDA succeeded in keeping the drug off the U.S. markets and received a lot of positive press. From this point onward, the



FDA demanded both efficacy and safety before granting final approval to market a drug. In 1997, Congress enacted section 561 of the FDCA, which permitted additional exemptions, on a compassionate basis, for treatment with investigational drugs outside the confines of an FDA-regulated clinical trial.

### *The Abigail Alliance*

If you ask a random group of people in the street whether a terminal patient, soon to die, should be allowed access to unapproved drugs before they are proven safe and efficacious, an overwhelming majority will probably say yes. In October 2005, the Abigail Alliance for Better Access to Development of Drugs, a citizens' group of terminally ill patients and their supporters, sued the FDA, seeking to challenge the regulatory policies for investigational drugs. The Abigail Alliance wanted patients whose physician had determined that their condition was terminal to have access to drugs that had passed Phase I of testing and that were now considered safe enough to move to Phase II (Okie, 2006). The case was heard before a three-judge panel of the U.S. Court of Appeals in Washington, DC. The Alliance attempted to establish an implied fundamental right that they said had already been secured by the Constitution, basing their claim on the guarantee to life and liberty in the Due Process Clause of the Fifth Amendment (Okie).

The Alliance asserted that, if terminal patients have an implied fundamental right to refuse treatment and die, a right that had already been granted by the U.S. Supreme Court (*Cruzan v. Director, Missouri Department of Health*, 1990), then that right should guarantee the choice to live and to pursue access to investigational drugs, if that is the only remaining alternative. The Alliance questioned whether Congress and the FDA had struck the right balance between early access and safety for the terminally ill (Kaufman, 2006).

The Abigail Alliance's lawsuit suggested to the FDA that there should be a "different risk-benefit trade off" for terminally ill patients with no other treatment options, as opposed to patients with treatment options. The efforts of the Alliance succeeded (Emmanuel, 2006), and in May 2006 they won their case by a two-to-one decision, ensuring dying patients the constitutional right to use any drug that had passed the first clinical test phase, as long as the pharmaceutical company agreed to make and sell or donate it. The drawback of the decision was that the drug company could not be forced to sell their drug, and in many cases, there would not be enough of a drug manufactured to distribute it outside of the clinical trials. The Alliance said their patients would purchase a drug if the sponsor was not willing to donate it ("Citizen Petition of the Abigail Alliance and the Washington Legal

Foundation,” 2006). The minority opinion, given by Judge Griffith, then questioned, “If a terminally ill patient has such a right, are patients with seriously ill conditions entitled to benefit from the same logic? If an indigent cannot afford potentially lifesaving drugs, then where is the justice?’ (*Alliance for Better Access to Developmental Drugs v Von Eschenbach*, 2006, p. 486).

The track record for drugs in very early phase trials has not been very encouraging. Of all the cancer drugs that enter clinical testing, only 5% are ever approved for patient use, and of the cancer drugs that move to Phase II, only 30% proceed to Phase III (Kola, 2004). Therefore, the odds that a drug in this early stage of testing will be safe and efficacious are slim, causing concern for the FDA about serious adverse events that might occur outside of a trial, further eroding the public’s faith in the drug approval process. Administration of these drugs by physicians who have little familiarity with the drug as far as dosage and the potential for side effects would create additional safety issues. Use of unapproved drugs would also be problematic for physicians, whose desire to help their patients conflicts with their ethical obligation to do no harm. Furthermore, there is the possibility of a malpractice suit, when serious adverse events or deaths occur. How would one differentiate between death caused by the experimental drug and death due to the natural progression of disease?

Most pharmaceutical companies have little incentive to sell unapproved drugs. Their concern focuses on the fact that adverse events could later be used to argue against FDA approval, halting manufacturing and denying use of the drug to future patients. Under FDA regulations, furthermore, patients cannot waive liability for negligence, leaving them the opportunity to sue doctors, drug companies, and the FDA (Howley, 2007). This is tremendous disincentive for all involved to sell or give away investigational drugs outside of a clinical trial.

As expected, the FDA was unhappy with outcome of the Abigail Alliance's lawsuit, and counter-sued. Federal officials filed an appeal, seeking to have the case reheard. Fifteen months later, on August 10, 2007, the full court, which had not been present for the first ruling, voted 8 to 2 that terminally ill patients who have exhausted all treatment do not have the constitutional right to use experimental drugs (Cannon, 2007).

#### *Congressional Support for Access to Unapproved Drugs*

Sam Brownback, a U.S. senator, agreed with the Abigail Alliance and introduced his own legislative proposal into the U.S. Senate in November 2005 (*Access, Compassion, Care, and Ethics for Seriously Ill Patients Act*, 2005). His intention was to make the regulatory policy work for dying patients. The purpose of the

Access, Compassion, Care and Ethics for Seriously Ill Patients Bill was to obtain tier 1 approval on the basis of Phase I testing and preclinical evidence from case histories, animal testing, pharmacologic studies or computer models that the drug may be effective against a life-threatening illness. Unlike the Abigail Alliance lawsuit, however, the patient waived the right to sue the drug sponsor (Okie, 2006, p. 439). This bill languished in the Senate and never became law. However, the quest continues with a second bill that was introduced by Congressman Christopher Shays, on September 29, 2006 (*Access, Compassion, Care, and Ethics for Seriously Ill Patients Act*, 2006). Shays' bill is an exact duplicate of Senator Brownback's and was introduced in the House of Representatives. There has been no ruling to date.

*Findings of Court Cases and Congressional Hearings Related to Public Access to Unapproved Drugs*

The following is a summary of the findings of the Abigail Alliance court case and appeal, and congressional hearings concerning the Access, Compassion, Care and Ethics for Seriously Ill Patients Bill and related bills. Rebuttals to the findings are also summarized.

*Finding.* Placebo-controlled studies are unethical for dying patients. (*Access, Compassion, Care, and Ethics for Seriously Ill Patients Act*, 2006).

Because cancer is a life-threatening illness, it is rarely ethical to give a placebo when something better than a placebo is available. Patients have to give informed consent to be in a trial, so they would know if the trial were using a placebo. In cancer trials, therefore, a new drug is tested along with a comparator or concoction of drugs approved for treatment of the disease. Given a choice, most patients diagnosed with cancer prefer the most recently discovered treatments (Lafferty, Bellas, & Corqage, 2004). A study of about 3000 active cancer trials in the National Institutes of Health Database showed that comparators, not placebos, were administered (Soares et al., 2005).

*Finding.* The current FDA drug approval process denies the benefits of medical progress to seriously ill patients who face morbidity or death, and there are unjustified delays and denials of approvals of promising therapies intended to treat serious life-threatening conditions (109th Congress, Second Session, 2006).

The FDA has many programs that expedite experimental drugs to seriously ill patients, usually during Phase II or later, rather than immediately following Phase I. The “compassionate

use” program allows physicians and their patients access to unapproved drugs outside of an FDA-approved clinical trial. Navigation of this program can be somewhat frustrating. However, in December 2006, the FDA leadership acknowledged these frustrations and proposed changes that will bring additional clarity to the process (Gottlieb, 2007). The changes clarify opportunities for the public to obtain drugs through compassionate/expanded use and other FDA programs, thus making treatment more widely available (Bristol, 2007). Allowing unfettered access to any therapy available was not considered a reasonable option.

The FDA grants either regular or accelerated marketing approval for oncology drugs (Johnson, Williams, & Pazdur, 2003). It is commonly believed that the FDA requires improvement in survival rate in order to approve a marketing application for a new oncology drug. However, most cancer drugs can now be approved based on surrogate endpoints, which shortens trials, since the sponsor does not have to show the drug is life saving (Schein, 2001). A surrogate endpoint consists of either halted tumor progression or shrinkage of tumor size. However, such a tumor response does not necessarily represent a cure or life-extension (Fleming & DeMets, 1996).

Regular marketing approval by the FDA does require substantial evidence of efficacy from adequate and well-controlled

clinical investigations. The attributes of these trials are explained in the FDA regulations (*Title 21 Code of Federal Regulations, Part 314.126*). Efficacy should be demonstrated by prolongation of life. Subpart H, which was added to the new drug application (NDA) regulations in 1992, allows accelerated approval (AA) for diseases that are serious and life-threatening, if the drug appears to show benefits over existing therapies. After FDA approval of the drug through AA, the sponsor must continue trials to demonstrate that treatment with the drug is indeed associated with clinical benefit. If this post-marketing study fails to show clinical benefit, then the drug will be taken off of the market (*Title 21 Code of Federal Regulations, Part 314.126, n.d.*). Twenty-six new cancer drugs for treatment of thirty different clinical indications received accelerated approval between 1995 and 2005 (Miller, 2007).

Single patient Investigational New Drug Applications may be used when the agent is available from the manufacturer, but there are no ongoing trials for the patient's particular cancer. If the patient's oncologist determines that there are no alternative medicines, the doctor can submit a request to the FDA for a Single Patient IND. The physician can now treat his or her patient with an unapproved drug (Cancer Liaison Program, n.d.).

Another exception is available under a Special Protocol Exception ("Subpart B: Investigational New Drug Application,"



n.d.). The patient is treated under the Sponsor's IND Application, with the patient's physician acting as an investigator. A patient who does not qualify for a trial because he or she does not have the type of cancer studied may have access to that drug outside of the trial. The patient's physician is responsible for all treatment and must provide follow-up information to the sponsor (IND applicant). The FDA rarely refuses an IND application if the requested protocol is reasonable and all other treatment options have been exhausted. The rate-limiting factor in this program is usually the urgency with which the patient's oncologist communicates with the FDA (Schwartz, 2007).

*Finding.* The Food and Drug Administration Advisory Committee should have greater representation of medical clinicians and laypersons to represent interests of seriously ill patients.

The FDA Oncologic Drugs Advisory Committee consists of nine oncologists, two oncology nurses, and one person with a Ph.D. in statistics (FDA U.S. Food and Drug Administration, 2007a). There is also an Advisory Committee of Consumer Representatives (U.S. Food and Drug Administration, 2007b). Consumer representatives play an important role in committee deliberations. This committee consists of representatives from interested consumers, consumer organizations, coalitions, and

associations that help to facilitate dialogue on scientific issues that affect all drug consumers. In addition, any individual can communicate with the FDA by commenting on new and revised FDA regulations through the Federal Register or through electronic dockets on their Web site, as well as by attending public meetings.

The FDA also has a Patient Representatives Program that is responsible for presenting the FDA with the individual and unique perspective of the patient and his/her family members (U.S. Food and Drug Administration, 2007c). The patient representative advises the FDA when products and therapies are presented for the diagnosis and treatment of cancer and HIV/AIDS. Patient representatives may also advise the FDA on products and therapies that relate to other serious and life-threatening diseases, on a case-by-case basis. The Office of Special Health Issues (OSHI), along with other FDA staff, assists the patient representative. The patient representative may serve as a voting or nonvoting member of an advisory committee and can be nominated by himself or by someone else (U.S. Food and Drug Administration, 2007c). The Patient Representatives Program could provide a means for members of the Abigail Alliance and other patient advocacy groups to have a voice in the FDA drug approval process and in gaining patient access to unapproved drugs.

*Finding.* The use of available investigational drugs for treatment is the responsibility of the physician and patient.

It is true that a patient's oncologist should have firsthand knowledge of the patient's disease and current situation. However, physicians of non-trial patients are not familiar with the dosing, metabolism, and possible adverse effects of an unapproved drug. By Phase II, the stage at which the Abigail Alliance wishes drugs to be made accessible to the public, only a handful of humans have been exposed to the experimental drug. The majority of adverse events do not usually show up until thousands of patients have used a drug for many months. This is the main reason for post-marketing surveillance (Strom, 2006).

*Objections to the Abigail Alliance and Congressional Bills Supporting Public Access to Unapproved Drugs*

In 2006, The National Coalition for Cancer Survivorship (NCCS), the American Society of Clinical Oncology (ASCO), and the Association of American Medical Colleges (AAMC) submitted an *amicus* (friend of the Court) brief to the Washington, D.C., Circuit Court of Appeals in support of the FDA (American Society of Clinical Oncology, 2007). Collectively, these groups stated that investigational drugs should not be commercially available,

because Phase I trials do not provide an adequate assessment of safety, let alone efficacy.

The Society for Clinical Trials, an organization committed to the development of reliable study designs for experimental drugs, voiced concern about the proposed legislation and its potential for substantial adverse events on public health (Society for Clinical Trials Board of Directors, 2006). Every drug that reaches Phase I testing looks promising; otherwise it would not be moving to Phase II. In reality, there are only a handful of breakthrough drugs among the hundreds under development at any given time (Begg, Brawley, Califf, & DeMets, 2006). Even if a cancer drug passes Phase I testing, only one in ten is approved for marketing (Parexel Corporation, 2005). The Society for Clinical Trials totally disagreed with the Abigail Alliance's criticism of the FDA's rigorous scientific method for drug approval, which is based on decades of experience (Begg et al., p. 155). This approach to drug testing is widely accepted by the scientific community, because the data obtained from randomized controlled trials provide conclusive and reliable data.

#### *A New Drug Is Not Always a Better Drug*

Given a choice, most patients diagnosed with cancer would probably seek out the newest treatment available to them, even if it

involved a relatively untried medication. In our culture, “new” usually implies better or improved. Yet, in medicine, this does not always turn out to be true. In drug development, therapeutic benefits are proven in randomized controlled trials (RCTs). As the practice of medicine becomes increasingly scientific and less accepting of unsupported opinion, the RCT has become the standard technique for changing diagnostic or therapeutic methods. Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Disease, stated that the goal of a RCT is “not to deliver therapy, it is to answer a scientific question, so that the drug can be available for everybody, once you have determined safety and efficacy” (Hellman & Hellman, 1999, p.1586).

In some cases, therapy regimens have turned out to be disastrous, especially those that have not been proven safe and efficacious by a previous RCT. This was the case with one of the highest profile treatments to be widely used outside the research setting before there was solid evidence that it was beneficial (Appelbaum, 1996). The treatment was high-dose chemotherapy combined with autologous bone marrow transplantation (HDC + ABMT), which was administered to patients with solid-tumor cancers, such as lung, breast, and ovarian cancer (Cheson, Lacerna, Leyland-Jones, & Sarosy 1989). Researchers thought that giving very high doses of chemotherapy would be the patients’ best hope.

After the chemotherapy, the transplant would return the bone marrow to normal. Data from very early studies led some researchers to conclude the new treatment was better than the standard treatment. A spokesperson for the National Cancer Institute (NCI; 2007) said that the preliminary evidence was very convincing, and those words spread through newspapers, such as the *New York Times*, like wildfire. Encouraged by this news, patients begged their doctors to prescribe and demanded that their insurance companies pay for the very expensive treatment. So many women received the therapy outside of the clinical trial process that it took years for investigators to enroll enough women to fill their RCT in order to determine which regimen really was superior (Welch, 2002). When, in 2000, results of the RCT began to trickle in, the results were sobering. Women who received the standard therapy did just as well as those that received the new HDC + ABMT therapy, with fewer complications and deaths (“High-Dose Chemotherapy,” 2000). Many of the complications were due to the high doses of chemotherapy and infections from bone marrow deficiencies, not from their cancers. For more than 10 years, desperately ill patients sought bone marrow transplantation as their last hope. Millions of health-care dollars and resources were wasted on an unapproved therapy regimen (Eddy, 1992). The *New York Times* published the sad truth: “As a society, we have to accept that rigorous evaluation

of new treatment is essential. Skipping this step may seem like a compassionate act, but it can have devastating consequences” (Eddy & Henderson, 1999, p. A17).

The case of HDC + ABMT demonstrates the problems that can arise and the suffering caused when drugs are used before they have been proven to be safe and efficacious through an FDA approved RCT. It also illustrates the difficulty of enrolling enough patients in trials to prove efficacy. There have been enormous strides in successful treatment of children with cancer, as a direct result of their high rates of participation in clinical trials. More than 60% of pediatric cancer patients take part in trials, while adult enrollment is only around 3% (National “Cancer Institute Cancer Clinical Trials: The In-Depth Program,” 2006). Increased enrollment of adults in clinical trials could greatly enhance the rate of cancer cures.

#### The FDA’s Critical Path Initiative

The FDA heard the pounding on their front door loudly and clearly, and knew that the drug development and approval process was in need of a serious overhaul. In March 2004, the FDA’s Critical Path Initiative was introduced, with the aim of organizing seventy-six science and regulatory areas to improve drug development (FDA, 2004). The stated goal was to enhance the

health and well-being of “all Americans.” The agency is using its unique position as a drug regulatory agency to work with other federal agencies, stakeholders, industry, patient groups, and academic researchers to identify scientific hurdles that are impairing the efficiency of evaluating and developing FDA-regulated products, with particular attention given to genetics-related drugs and new diagnostic tools.

The Critical Path Initiative is continually evolving. The FDA has undertaken efforts to reduce the time spent in early drug development, thus enabling new medical discoveries and promising drugs to move from the laboratory to the consumer more efficiently, while maintaining protection of human subjects (“FDA’s Critical Path Initiative Science Enhancing the Health and Well-Being of All Americans,” 2004). The agency aims to realize more and faster public health benefits through the modernization of computer models, *in vitro* tests, qualified biomarkers, and innovative study designs, which will move the FDA drug development and evaluation process into the 21st century (von Eschenbach, 2007).

### *Clinical Trials of New Drugs*

Today, the vast majority of patients in the United States with life-threatening diseases are treated with drugs that have passed



the FDA's stringent evaluation process, designed to ensure that the drugs are safe and effective. Drug trials conducted in the U.S. are the most rigorous in the world. The two main drug characteristics examined during a clinical trial are safety and efficacy. The five main points investigated are (a) do the benefits of the drug outweigh the risks; (b) once the trial has begun, should it be continued, based on reports of side effects and effectiveness of the treatment; (c) at the completion of the trial, should the drug be sold to the public; (d) what claims can the manufacturer make; and (e) what should the labels say, as far as directions for use, side effects, and warnings (von Eschenbach, 2007). Although efforts are made to reduce risks to participants in clinical trials, some risk is unavoidable due to the uncertainty inherent in clinical research involving new medical products. Each phase of a trial has a specific purpose, and the potential for benefits, risks, and harm, may vary among different phases.

Historically, the implementation, design, and analysis of clinical trials have followed well-established guidelines and statistical principles to accurately and objectively determine differences between experimental and control groups. However, the FDA is aware of the need for new strategies in the battle against cancer. Cancer is caused by specific changes or mutations in one or more of twenty to twenty-five thousand genes, especially genes

that produce substances that influence cell division (Nathan, 2007). The significant genetic and metabolic differences among individual cancers need to be considered in designing trials and appropriate drug regimens. Genetic differences among individual patients may increase or decrease the risk of disease and affect their response to treatments. A complex and heterogeneous disease, cancer requires targeted therapies that demonstrate consistent anti-tumor response early in efficacy trials. Cancer trials are slowly progressing from the use of cytotoxic, or cell-killing, drugs that not only kill cancer cells but also destroy many healthy cells, to smart drugs that target specific tumor types and block molecular pathways. Early Phase I studies using tools that profile gene-expression–gene-sequencing, proteomics, and molecular imaging can identify subgroups of patients who are likely to respond to a new drug or therapy (Roberts, 2004). Thus, patients in earlier trial phases will see more improvements in their cancers.

Cancer patients who use experimental drugs outside of a clinical trial, on the basis that it worked for other patients with the same type of cancer, face high odds that the drug will not work for them because of genetic differences in their cancers (“Price Water House Coopers, 2005). Genetic differences may also render certain

patients more susceptible to serious adverse effects of an experimental drug.

### *Phase Zero Cancer Trials*

In January 2006, the FDA announced new rules that would allow small doses of experimental drugs to be tested on people before full-scale clinical trials. Such phase zero trials are designed to evaluate the pharmacodynamic (PD) effects of candidate drugs at the molecular level in the clinic. The trials will use biopsies of target tissues to determine the quantitative effect of the drug after a minimum number of doses. This method will require repeated tumor biopsies, as well as some knowledge of the dose level likely to cause a tumor response (Kinders, 2007).

Phase zero studies do not examine safety or effectiveness; instead, they gather data on the targeting action and metabolism of the drug in the body. These trials are designed to be short and use a very small number of human subjects, who are given very low doses of the drug. Phase zero trials will allow drug manufacturers to identify failing drugs early in the testing process and will generate data that can be used to design smarter Phase I trials for promising drugs. Phase zero trials are an improvement over the use of animal data alone as the basis for selecting drugs for Phase I trials. Woodcock (n.d.), the FDA's Deputy Commissioner for Operations, views phase zero trials as a way to protect patients by decreasing human exposure to compounds that ultimately

fail, which at this point includes the majority of experimental cancer drugs.

### *Adaptive Drug Trials*

Adaptive drug trials are an example of the FDA using better technology and better science to speed cancer drugs through the trial process. In a regular phase trial of a new cancer drug, the drug is administered to a group of patients with various types of the disease, with the hope that a percentage of them will benefit. In contrast, an adaptive trial begins with a heterogeneous group of patients and then adds patients with a particular type of disease, as data from outside the trial suggest that these specific patients are most likely to benefit (Groopman, 2006). Instead of waiting until the end of the trial, the data are analyzed after partial enrollment. New patients are added to the subgroup of patients that shows the best response rate. For example, if the response rate is twice as high in one subgroup, then twice as many patients will be enrolled in that subgroup. Thus, patients benefit from the knowledge gained during the trial, instead of having to wait for completion of the trial (Galloway, 2005). Scott Gottlieb (2006), an FDA Deputy Commissioner, has stated that the FDA will receive criticism for cutting corners; however, in the case of cancer patients who are willing to take more risk, adaptive trials are acceptable.

### *The Use of Bayesian Statistics in New Drug Trials*

A finding in the Brownback Bill (2005) criticized the FDA for relying on antiquated statistical methods that slowed drug development. Therefore, Bayesian statistics are now being used in many Phase I and Phase II trials at the National Cancer Institute. This statistical method assigns a probability to unknowns, using information from previous experiments. As in adaptive trials, information is continually being updated. Doctors using this approach are able to look at multiple treatment combinations and determine patient response by looking at the effect of the drug on particular cancer biomarkers (Berry, 2006).

### *Targeted Cancer Therapies*

As a general rule, chemotherapy for any cancer has been based on a one-size-fits-all approach. However, there are now a wide range of available technologies, such as genomics and proteomics that are used in the development of new targeted drug treatments. Targeted therapies use drugs that block the growth and spread of cancer by interfering with specific molecules that are involved with the process by which normal cells become cancer (National Cancer Institute Targeted Cancer Therapies, 2007).

Trials of a targeted therapy may be run as early as Phase II of drug testing. Subpart H of the Code of Federal Regulations [21 CFR 314.510] allows drugs to be approved on the basis of surrogate endpoints. In the

case of a cancer trial, the surrogate endpoint would usually be tumor shrinkage or lack of advancement in size of the tumor. New imaging technology has made such endpoints easier to determine. Thus, cancer patients with unmet needs now have access to drugs that have demonstrated effectiveness against a surrogate marker that is “reasonably likely” to predict clinical benefit, based on an endpoint other than survival or irreversible morbidity.

### Conclusion

The FDA has admitted that the process of approving new drugs and transforming new technologies developed in clinical laboratories into safe and effective treatments available to all patients has been slow and difficult. Driven by the hope of a “breakthrough,” cancer patients are increasingly trying to gain access to experimental drugs before the drugs have received FDA approval. However, giving patients access to drugs that are in the early stages of testing is dangerous and undermines the integrity of the clinical trial system by slowing enrollment. Thus, providing access to unapproved drugs to a few patients may actually slow the access for all patients.

Through the Critical Path Initiative, the FDA has identified specific problems and is taking steps to move the drug approval process and clinical trial system into the 21<sup>st</sup> century. Acknowledging that perfecting the system will take years, the FDA has made many drugs available to

terminal patients through compassionate use programs. However, the importance of the clinical trial system in developing and testing new drugs for safety and efficacy cannot be overstated. For most cancer patients who have failed all approved forms of therapy, the safest way to access investigational drugs is through an FDA-approved clinical trial.

## References

- 109th Congress, Second Session. (2006). *Bill H.R 6303* House of Representatives. Retrieved September 29, 2007, from [http://www.capitolresearch.us/reports/2005energy\\_policy.html](http://www.capitolresearch.us/reports/2005energy_policy.html)
- Abigail Alliance for Better Access to Developmental Drugs v Von Eschenbach*.(2006). Retrieved September 16, 2007, from <http://www.wlf.org/upload/010407RS.pdf>
- Access, compassion, care, and ethics for seriously ill patients act*. (2006). Retrieved September 16, 2007, from <http://www.sctweb.org/positionpapers/S.1956-clinical-trials.pdf>
- American Society of Clinical Oncology (ASCO). (2007). Physician and patient care groups join to support FDA over access to experimental drugs. Retrieved October 1, 2007, from <http://www.asco.org/portal/site/ASCO/menuitem.6221d9cbf019a5ed6d5ba10320041a0/?vgnextoid=a9>
- Appelbaum, F. R. (1996). The use of bone marrow and peripheral blood stem transplantation in the treatment of cancer. *CA: A Cancer Journal for Clinicians*, 46, 142-164.
- Begg, C., Brawley, O., Califf, R., & DeMets, D. (2006). The society for clinical trials opposes U.S. legislation to permit marketing of unproven medical therapies for seriously ill patients. *Clinical Trials*, 3, 154-157.



Berry, D. (2006). New statistical method needed for clinical trials current approach has flaws one researcher says. Houston, TX: Anderson Cancer Center.

Bristol, N. (2007). Should terminally ill patients have access to Phase I drugs? *Lancet*, 369, 815-816.

Brownback Bill. (2005) Retrieved October 15, 2007, from <http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/04-10-2002/0001703577&EDATE>

Cancer Liaison Program. (n.d.). Retrieved October 4, 2007, from <http://www.fda.gov/oashi/cancer/cancer.html>

Cannon, M. (2007). *A snub for the dying*. Retrieved October 4, 2007, from <http://www.cato-at-liberty.org/2007/08/10/a-snub-for-the-dying/>

Cheson, L., Lacerna, B., Leyland-Jones, G., & Sarosy, A. (1989). Autologous bone marrow transplantation: Current status and future directions. *Annals of Internal Medicine*, 110 (3), 51-65.

*Citizen petition of the Abigail Alliance and the Washington legal foundation*. (2006). Retrieved September 25, 2007, from [http://www.abigail-alliance.org/WLF\\_FDA.pdf](http://www.abigail-alliance.org/WLF_FDA.pdf)

*Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261. (1990). Retrieved September 25, 2007, from

- <http://www.law.umkc.edu/faculty/projects/ftrials/conlaw/cruzan.html>
- Drugs and Food under the 1938 ACT and Its Amendments*. Retrieved September 21, 2007 from [www.fda.gov/oc/history/history/offda/section3.html](http://www.fda.gov/oc/history/history/offda/section3.html)
- Eddy, D. M. (1992). High-dose chemotherapy with autologous bone marrow transplantation for the treatment of metastatic breast cancer. *Journal of Clinical Oncology*, 10, 657-670.
- Eddy, D. M., & Henderson, C. (1999, April 17). A cancer treatment under a cloud. *New York Times*, A17.
- Emmanuel, E. J. (2006, July 3). Cancer In the courts drug addiction. *The New Republic Magazine*, 4-5,.
- FDA. (2004). U.S. department of health and human services innovation-stagnation, challenge and opportunity on the critical path to new medical products. Retrieved September 25, 2007, from <http://www.fda.gov/oc/initiatives/criticalpath/initiative.html>
- FDA's critical path initiative science enhancing the health and well-being of all Americans. (2004). Retrieved September 25, 2007, from <http://www.fda.gov/oc/initiatives/criticalpath/initiative.html>
- Fleming, T. R., & DeMets, D. L. (1996). Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine*, 125(7), 605-613.
- Galloway, D. (2005). Biostatistically speaking. *OncoLog*, 50 (2/3), 1-2.

- Groopman, J. (2006, December 18). The right to a trial should a dying patient have access to experimental drugs. *The New Yorker*, 11.
- Gottlieb, S. (2006, July). FDA. Speech presented before 2006 Conference on Adaptive Trial Design , Washington, DC. Retrieved October 16, 2007, [http://www.aei.org/publications/ filter.All .msgkey.20038142220000243.pageID.243/default.asp](http://www.aei.org/publications/filter.All.msgkey.20038142220000243.pageID.243/default.asp)
- Gottlieb, S. (2007). Improving access to life saving medicine through modernization of regulatory review. Retrieved September 15, 2007, from [http://www.aei .org/publications/filter.all.msgkey .20038142220000243,pageID.243/default.asp](http://www.aei.org/publications/filter.all.msgkey.20038142220000243.pageID.243/default.asp)
- Harris, S. (2007). AAMC reporter court rejects claim to experimental drug access. Retrieved September 7, 2007, from [http://www.aamc .org/newsroom/ reporter/sept07/drugaccess .htm](http://www.aamc.org/newsroom/reporter/sept07/drugaccess.htm)
- Hellman, S., & Hellamn, D. (1991). Of mice but not men: Problems of the randomized clinical trial. *New England Journal of Medicine*, 324, 1585-1589.
- High-dose chemotherapy plus autologous bone marrow transplantation for metastatic breast cancer [Editorial]. (2000). *New England Journal of Medicine*, 342. 119-1121.
- History of the FDA*. (2006). Retrieved September 15, 2007, from <http://www.fda.gov/oc/history/historyoffda/section2.html>

- Howley, K. (2007, August-September). Dying For lifesaving drugs. Will desperate patients destroy the pharmaceutical system that produces tomorrow's treatment? *Reason Magazine*, 10.
- Johnson, J., Williams.,G., & Pazdur, R. (2003). End points and United States food and drug administration approval of oncology drugs. *Journal of Clinical Oncology*, 21, 1404-1411..
- Kaufman, M. (2006, May 3). Court backs experimental drugs for dying patients. *Washington Post .com*. Retrieved September 25, 2007, from [http://www.washingtonpost.com/wp-dyn/content/article/2006/05/02/AR20060205201470\\_p...](http://www.washingtonpost.com/wp-dyn/content/article/2006/05/02/AR20060205201470_p...)
- Kinders, R. J. (2007). Developmental therapeutics: Preclinical modeling of a phase 0 clinical trial protocol meeting. ASCO Annual Meeting Abstract No: 14058
- Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3, 711-716.
- Kurian, G. (Ed.). (1998). *The historical guide to American government*. New York: Oxford University Press.
- Lafferty, W. E., Bellas, A., & Corqage, B. A. (2004). The use of complementary and alternative providers by insured cancer patients in Washington State. *Cancer*, 100, 1522-1530.
- Milestones in U.S.FDA food and drug law history. (1999). Retrieved October 16, 2007, from <http://www.fda.gov/opacom/backgrounders/miles.html>

- Miller, R. (2007, August 1). Cancer regression . *The Wall Street Journal*, p. A.15.
- Nathan, D. (2007). *The cancer treatment revolution*. Hoboken, NJ: Wiley.
- National Cancer Institute. (2007) *Understanding the approval process for new cancer treatments*. Retrieved September 4, 2007, from <http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/allpages/print>
- National Cancer Institute Cancer Clinical Trials: The In-Depth Program* (2006). Retrieved November 3, 2006, from <http://www.cancer.gov/clinicaltrials/resources/in-depth-program/page2>.
- National cancer institute targeted cancer therapies* (2007). Retrieved October 22, 2007, from <http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted>
- Parexel Corporation. (2005). *Parexel sourcebook*. Waltham, MA: Author.
- Price Water House Coopers. (2005). *Personalized medicine: The emerging pharmacogenomics revolution*. Retrieved September 11, 2007, from <http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf>
- Roberts, T., & Chabner, B. (2004). Beyond fast track for drug approvals. *New England Journal of Medicine*, 351,501-505.
- Schein, P. S. (2001). The case for a new national program for the development of cancer therapeutics. *Journal of Clinical Oncology*, 19, 3142-3153.

Schwartz, K. (2007). *Compassionate use of investigational therapies*.

Retrieved October 16, 2007, from [www.lymphoma.org](http://www.lymphoma.org)

Soares, H. P., Kumar, A., Daniels, S., Swann, S., Cantor, A., Hozo, I.,

Clark, M., et al. (2005). Evaluation of new treatments in radiation oncology: Are they better than standard treatment? *Journal of the American Medical Association*, 293, 970-978

Society for Clinical Trials Board of Directors. (2006). The Society for Clinical Trials opposes U.S. legislation to permit marketing of unproven medical therapies for seriously ill patients. *Clinical Trials*, 3, 154-157.

Strom, B. L. (2006). How the U.S. drug safety system should be changed

*Journal of the American Medical Association*, 295, 2072-2075.

Subpart B Investigational New Drug Application (IND) 312.20. (n.d).

Retrieved September 23, 2007, from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312>

*Title 21 Code of Federal Regulations, Part 314.126*. (n.d.). Retrieved

October 16, 2007, from [http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title21/21cfr314\\_main\\_02.tpl](http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title21/21cfr314_main_02.tpl)

*Title 21 Code of Federal Regulations, Part 314.93* (n.d.) Retrieved October

28, 2007, from [http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title21/21cfr314\\_main\\_02.tpl](http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title21/21cfr314_main_02.tpl)

- U.S. Food and Drug Administration. (2007a) CDER Advisory Committee Consumer Representatives. Retrieved September 25, 2007, from <http://www.fda.gov/oc/advisory/consumer.html>
- U.S. Food and Drug Administration. (2007b). CDER FDAA Patient Representative Program. Retrieved September 25, 2007, from <http://www.fda.gov/oashi/patrep/patientrep.html>
- U.S. Food and Drug Administration. (2007c). CDER, Oncologic Drugs Advisory Committee Roster. Retrieved September 25, 2007, from <http://www.fda.gov/cder/audiences/acspage/oncologicroster1.htm>
- von Eschenbach. (2007). Field hearing. Retrieved June 1, 2007, from <http://www.fda.gov/ola/2007/criticalpath060107.html>
- Welch, G. (2002). Education and debate presumed benefit: Lessons from the American experience with marrow transplantation for breast cancer. *British Medical Journal*, 324, 1088-1092.
- Woodcock, J. (n.d.). *Discovering new medicines for better lives and brighter futures*. Retrieved October 1, 2007, from <http://www.innovation.org>