Legal Backgrounder

WLF Washington Legal Foundation

Advocate for freedom and justice®
2009 Massachusetts Avenue, NW
Washington, DC 20036
202.588.0302

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MAKING FDA WORK FOR PATIENTS

by

Steven Walker

As a nation, we are accustomed to scientific progress. The advances of the last century have, for example, allowed us to live years longer in better health, and brought us new medical treatments that can cure or control a variety of previously limiting or fatal diseases.

Now, during this period of unprecedented success, patients face a regulatory crisis of massive proportions. Our regulatory system has failed to evolve with the advancing science, leaving us with a drug development and approval process no longer capable of effectively protecting and promoting the public health. At the center of this crisis is the U.S. Food and Drug Administration (FDA).

A vast number of patients are being left out of medical progress — progress inhibited by a federal agency which tells dying patients that waiting, and dying while they wait, is in their best interests.

Background. In the 1970s, the United States made a national commitment to basic medical research and has steadily increased funding for those efforts through the present. Over the last 25 years, federal policy has also recognized the potential of the private sector to accelerate medical progress by utilizing its capital and efficient product development models to tackle the most difficult part of the process: transforming basic research discoveries into usable treatments. In the 1980s and 1990s, in an effort to boost industry and investor interest, Congress passed a series of laws creating incentives for private-sector investment in development of new and better treatments.

This focus on basic research and engaging the private sector is now paying off. New information regarding causes and possible treatments for a variety of serious diseases is emerging from our basic research laboratories into the hands of public- and private-sector organizations that can transform such knowledge into safe and effective new treatments.

In the meantime, the FDA has been relying on a drug development and approval model conceived decades ago. In the early 1960s, realizing that science does not always succeed, and that pharmaceutical companies and physicians are fallible, Congress modified the Food, Drug and Cosmetic Act to require the FDA to determine that new medicines are both safe *and* "effective." Until then, the FDA had long been regulating drug safety, but had no mandate to evaluate effectiveness.

At that time, biomedical knowledge and the technology needed to broaden it were crude by today's standards. Drug discovery proceeded largely by trial and error, screening thousands of compounds to find a few that worked in a lab, and perhaps one that eventually could serve as a viable treatment. Researchers were flying blind. The state of the art also limited the options available to the FDA, leaving the regulators with no choice but to devise equally primitive methods for measuring effectiveness.

Steven Walker is Regulatory Advisor to the Abigail Alliance for Better Access to Developmental Drugs, an Arlington, Virginia-based patient group dedicated to helping cancer patients and others with life-threatening and serious diseases.

The basic elements of our comparative clinical trials system are fourfold. Researchers first determine (using a small number of volunteers) an appropriate dose and whether the drug appears to be safe at that dose (i.e., substantially less dangerous than the condition it was intended to treat). Next, the drug is tested in a larger number of patients with the specified condition. It is then given to an even larger number of people with the condition and compared to a similar number of people with the same condition, called controls. Control group patients might receive nothing, a placebo (sugar pill), or an already-approved drug known to work at some level for the same condition. Finally, the outcomes for the two groups are compared and the results are used to evaluate whether the new drug is more effective than nothing, or at least is as effective as an older drug. If it is found to be acceptably safe and works at some level based on these standards, also called endpoints, the FDA may approve it.

The data produced from the clinical trials are well suited to evaluation using the mathematical tool of statistics, and FDA adopted the rules of statistics from the outset as the basic drivers for clinical trial design and analysis of trial results. The thinking was to structure the trials in such a way that the data produced would be amenable to statistical analysis and would meet its theoretical tests for validity. As the field of human clinical testing evolved, the trials were increasingly designed to facilitate the strengths and also the severe limitations of statistical analytical techniques. Simultaneously, the FDA established increasingly detailed and rigid standards governing approval decisions for new treatments. These standards were largely statistical in nature, hinging on artificial measures of data validity called "probability values" and "confidence limits." Another requirement of the statistical approach was the need to compare "apples to apples" in the clinical trials, resulting in the parsing of a single disease (*e.g.*, colon cancer) into many disease sub-types for which an isolated approval could be obtained.

On the positive side, this approach did not require the FDA to know for certain what caused the disease being treated or what the new drug was doing to treat it. In other words, it enabled the FDA to be "science-blind." In a time when those things were often unknowable, a phased clinical trials system would still allow the FDA to achieve its mission of protecting and promoting the public health. Another plus for regulators was that because the statistical approach did not require any detailed scientific knowledge or clinical skills, decision-making based on sound scientific and clinical judgment was not required or even allowed. The removal of these factors from the approval process relieved decision-makers at the FDA from any direct accountability for approving a drug that later proved to be unsafe, or for delaying approval of a new treatment that could have saved many lives.

On the negative side, the FDA's focus on fine points of statistical methodology in making approval decisions for new treatments caused the trials to be designed with restrictive entry criteria that excluded many patients from participation. Perhaps the most damaging effect of the focus on statistical methodology was that it often had the effect of banishing from the approval process consideration of the real science underlying the disease and the drug.

The science-blind approach to drug assessment has also fostered a risk-averse culture at the FDA, one strongly favoring the invisible mistake of delaying the approval of safe and effective treatments to minimize the chance of making a highly visible mistake — approving an unsafe or ineffective drug that must later be withdrawn. The way the FDA is organized has reinforced this risk aversion. It is an organizational structure where responsibility for decisions and performance is spread thin and wide across a number of disciplines and offices. This structure provides little incentive for any one reviewer to step outside his or her own chute of responsibility into the path of accountability. When mistakes happen, the agency invokes a rote defense — procedures and policies were followed, statistical standards were met, and therefore the mistake was unavoidable. No one individual is responsible because no one individual can be responsible.

The Effect. The process of moving new discoveries from the laboratory to the bedside is called "translation," and there is widespread agreement that we are failing to convert an unprecedented expansion of scientific knowledge into more effective treatments. There is considerably less agreement on why we are failing, mainly caused by a near cult-like belief in the purity of statistical methodology in the drug approval

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process. In this new age of "smart science" drug invention, we are haltingly laboring ahead with a decades-old science-blind translation system.

The FDA has worked diligently to preserve and entrench its primitive methods, even as the field it regulates surpasses it. Had the FDA kept pace, we would now be evaluating and approving some new drugs and treatments based on our knowledge of the causes of disease, and direct observation of how a new drug affects the cause. We would be using science-based facts obtained from direct observation with small, scientifically-driven clinical trials designed to confirm reasonable safety and effectiveness rather than to establish it, and we would follow up after approval of a new treatment with long-term monitoring in actual patient populations.

Unfortunately, the FDA claims to have no idea how to do this and has begun well-intentioned but unfunded initiatives called "Critical Path" and "Stimulating Innovation" to try to figure it out. In typical fashion, the agency has reviewed its practices and the field in general, and concluded that most of the problems lie beyond its walls. Until the FDA realizes that the organizations outside the FDA are simply responding to its mandates, sponsors trying to translate discoveries to patients will have to make do with the FDA's science-blind approach.

The Patients. As the FDA continues to stand still, encumbered with a bureaucratic resistance to change, it remains a drag on medical progress and a lethal barrier to a vast number of terminally-ill Americans trying to gain access to that progress. Those patients invariably find themselves fighting two adversaries: their life-threatening disease and the FDA's "process before patients" system in which serving the best interests of patients is secondary to the FDA's inflexible policies and practices.

Every year more than one-half million Americans die in the U.S from cancer alone. As recently as ten years ago, there was little to be done. The pipeline of new cancer drugs showing evidence of effectiveness was sparsely filled. The focus of most clinical trials was to find new ways to use a small number of existing drugs already known to be inadequate, and progress was being made in rare, tiny steps. According to experts, cures were many decades away.

By the mid-1990s, however, a first wave of knowledge-based, smart science cancer drugs were entering the FDA's clinical trials process, with many more in pre-clinical development. That number has now grown to several hundred highly-innovative investigational treatments in clinical trials today. The new drugs are variable in their genesis and design, reflecting the diverse nature of scientific advances. In cancer, they consist of small chemicals designed to block receptors on cancer cells, manufactured biological antibodies designed to gum up cancer cell signaling mechanisms, and even biological molecules attached to small radioactive particles that are injected into the bloodstream where they seek out cancer cells and deliver the radiation directly to the tumors. Some show startling evidence of safety and effectiveness in early testing, but take years to reach patients as they travel the tortuous path of the FDA's outmoded drug development and approval system.

One of these new creations, and its path to patients, provides a telling example of the problem. A drug called STI-571 (now known as Gleevec) worked so well for patients in a small Phase I trial, many labeled it a new miracle cancer drug. In 1998, all 31 patients in the trial experienced dramatic positive responses to the drug without any serious side-effects. Tragically, instead of being delivered immediately to patients with a highly-lethal form of leukemia, the FDA required a Phase II trial as a matter of pro-forma policy before the drug could be made available to anyone outside a clinical trial. Some patients eventually got the drug before it was approved based on data collected in the Phase II trial and a program known as "compassionate use." Many patients, however, died waiting for the FDA to approve Gleevec; an approval that didn't come for more than two years after its safety and efficacy were well established. It has since proven to be effective in treating at least one additional form of lethal cancer, and other life-saving and life-extending uses for the drug appear likely to emerge.

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Thanks to the ineffectiveness of FDA policies governing clinical trials and approval standards, the Gleevec scenario has repeated itself numerous times in the last seven years where drugs have been discovered to be safe and effective against a variety of deadly cancers shown in early and even late-stage clinical trials. The FDA's staunch resistance to change has led to slowed and even stalled progress against cancer and other deadly diseases, and a mounting toll of shortened lives that may now number in the millions.

Despite the obvious and increasing collision between scientific progress and the FDA's failure to keep up, the agency has yet to implement a single change resulting in direct benefit to patients, opting instead to begin studies and initiatives that will take years to yield results. In the meantime, its forty-year-old assessment process remains in place, and a vast number of patients die every year waiting for medical progress already made to reach them.

The recently reported safety problems with pediatric anti-depressant drugs and with the pain reliever Vioxx arose from the same fundamental shortcomings that cause the FDA to routinely delay approvals for breakthrough cancer treatments.

Simply put, statistics is a set of powerful mathematical tools scientists use to help them test or understand data from their experiments, but statistics are almost never used as the *only* basis for making decisions. Statistical methods alone give a limited view of scientific data when they lack an understanding of the underlying scientific phenomena. Yet the FDA has built its entire system of drug development and approval around just that approach. The result is an FDA operating with outdated, ineffective regulations and policies that drive up the cost of medical progress and prevent the delivery of that progress to those who need it most: patients suffering from serious and terminal diseases. The agency needs new decision-making tools and approval authorities that are based on real science, not just statistical measures like "p-values" and "confidence limits." If you don't know what a p-value or confidence limit is, you just might be better at recognizing and approving new breakthrough cancer drugs than the FDA, saving a lot of lives as a result.

Possible Solutions. The Abigail Alliance for Better Access to Developmental Drugs and its counsel, the Washington Legal Foundation, have proposed a regulatory reform called "Tier 1 Initial Approval." It is designed to make promising new treatments available to terminally-ill patients in a time frame meaningful to them — that is, while they are still alive. The program would allow drug sponsors to sell an investigational drug (a drug undergoing clinical trials in humans) to patients with life-threatening illnesses who have not been able to gain entry into a clinical trial. Those patients would thus have an opportunity to take the same risks, and seek the same potential benefits, as patients in the clinical trials. Tier 1 is a comprehensive proposal intended to improve patient access to medical progress while protecting the clinical trials system, providing incentives for sponsor participation, and creating a potential for insurance coverage and patient assistance programs to cover the cost of Tier 1 drugs for patients reasonably choosing to pursue better, longer lives. A petition asking for adoption of the new authority was submitted to the FDA on June 11, 2003. The petition shows in detail that such a program is within the FDA's statutory authority and does not require new legislation.

On July 28, 2003, the Abigail Alliance and the Washington Legal Foundation filed a lawsuit in federal court against the FDA and its parent agency, the U.S. Department of Health and Human Services, asking for a ruling that the FDA's policies violate the constitutional rights of terminally ill patients with no approved treatment options by depriving them of life and liberty without due process and by infringing on their right to privacy. The U.S. District Court for the District of Columbia rejected these constitutional arguments in an August 30, 2004 ruling, and the case is now on appeal.

Ultimately, the remedy for overcoming the regulatory barriers between promising new medicines and the dying patients who desire them rests with a cultural change within FDA: a perspective in which the agency considers itself at fault when it makes a mistake in delaying an important new medicine no less than when it makes a mistake in approving a new medicine. How to bring this cultural shift about is the major challenge facing lawmakers and agency leaders.

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