

Impact of FDA Regulation on Oncology Drug Research and Development

by

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Introduction

In the United States, cancer is the second leading cause of death across all ages and the most common cause of death for people under age 85 years (1). It is estimated that about 559,650 Americans will die from cancer in 2007 corresponding to about 1,500 deaths per day. In addition to mortality, cancer leaves many individuals with chronic and often incapacitating disabilities, not to mention the fear and emotional despair associated with the diagnosis. President Nixon passed legislation in 1971 creating the “War on Cancer” imposing a national commitment to its control and potential eradication. Increased government funding catalyzed more intensive research leading to a better understanding of cancer and improved diagnostics and treatments. According to an American Cancer Society 2006 report, cancer mortality rates have been declining in the U.S. by 1% per year since 1990 (2).

There is growing concern, however, that the pace of cancer research and its translation to useful new products for patients may be slowing or is inconsistent. For example, while a decline in mortality has been steep for breast and colorectal cancer among women and for prostate, colorectal and lung cancer among men, trends for all other cancer sites have declined at a much slower rate.

Several studies indicate a general slowing of new drug approvals despite substantial increases in biomedical research funding from government and industry. These concerns prompted FDA to issue its report in March 2004, “Innovation Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products (3).” Despite a ten year increase in inflation-adjusted research spending of over 150%, submission of new drug applications and approval of new molecular entities has declined according to a report from the United States Government Accountability Office (GAO, 4). These trends have been attributed to a current medical product development path that has become increasingly challenging, inefficient and costly. FDA has admonished industry to apply new science and technology to better guide product development and reduce the current inefficiencies, due in large part to reliance on outdated and cumbersome methods.

The incentives to conduct research, develop and commercialize new and improved oncology drugs will depend on costs, risks and product development time. In this publication, I report on the issues facing

biopharmaceutical companies researching and developing novel therapeutic products for cancer. As will be presented, these issues are a serious threat to continued progress in the fight against cancer.

Perspective on Issues Facing Oncology Drug Development

Oncology drugs are different. Sixty-eight new oncology drugs were approved by the FDA between 1990 to 2005 (5). Several of these drugs are in the supportive care category such as hematopoietic growth factors. As shown in Table 1, from a regulatory perspective, oncology drugs differ substantially from other new drugs. Seventy-one percent of oncology drug approvals were given priority review status by FDA and nearly half received orphan drug designation. These characteristics reflect Congressional action taken in the early 1990s to expedite the development of drugs intended to treat life-threatening diseases such as AIDS and cancer. This legislation produced regulations such as Priority Review, Fast-track designation, Accelerated Approval and Orphan drug designation. For example, oncology drugs are disproportionately given priority ratings by FDA leading to faster review of marketing applications. FDA reviews oncology drugs, on average, 6 months faster than other drugs (5).

Development time and expense. Despite the priority given to oncology drugs, the development times and rate of approvals are unfavorable compared to other drugs. Median clinical trial durations are 1.5 years longer for oncology drugs, 7.8 years vs. 6.3 years (5). Oncology drugs transition to the more expensive phase 2 and phase 3 trials more frequently than other drugs yet have a lower rate of approval. The overall approval rate for oncology drugs entering phase 1 clinical development is 8% compared to 20% for other drugs (6).

Clinical trials are becoming larger and more expensive. Since 1980, the average number of clinical trials conducted to support an NDA has more than doubled, from thirty to about seventy. Likewise, the average number of patients required to support an NDA has almost tripled, from 1,576 in the late 1970's to 4,237 in the mid 1990's, and the number of medical procedures performed during the clinical testing rose 61 percent from 1992 to 1997 (7). In an analysis done by Hirschhorn, the average number of patients participating in clinical trials per NDA increased 19% during the period 1995 to 2001 (8).

In addition to the increasing number of patients required for clinical trials, costs of clinical efficacy assessments have increased as clinical investigation moves more towards establishing proof of clinical benefit as well as the demonstration of survival benefit. CT, MRI and PET scans, quality of life assessments and other sophisticated evaluations have increased the cost of clinical trials. Additional required safety studies also have contributed to higher costs such as studies on drug interactions, drug safety in special populations and drug effects on cardiac electrophysiology (known as the Q-T interval).

Increasing bureaucracy and inefficiency. Clinical investigation is becoming more bureaucratic. Dilts, et al. studied the procedures and policies required to activate phase 3 studies sponsored by the Cancer and Leukemia Group B (CALGB), a large and prestigious cooperative clinical research group funded by the National Cancer Institute (NCI). They examined thirteen clinical trials in the period 2002-2005 and found that the median time to activate a study was 580 days (range, 295 days to 1,248 days) from protocol concept to approval and 784 days from initial conception of the study (9). More than 370 distinct steps, 30 groups or individuals, 70 signatures, 40 decision points and 30 processing loops were required for study activation. About half of the steps did not add any value to the protocol and no protocol made it through the entire process without the need for revision and repeated review. For any phase trial, it takes a median of 172 days to open a clinical study, indicating that, in a best case, at least 1.5 years are spent on administrative matters taking a drug through phase 1,2 and 3 trials (10). Increasing administrative burdens are incremental to those required by FDA and result, not only, from requirements imposed by institutional medical review boards, but by the increasingly conservative position of institutional grants and contracts offices.

Discouragingly, many open studies do not enroll sufficient patients to answer the questions posed by the trial. Dilts found that more than one in five studies (20.6%) accrued no patients and more than half (53.7%) enrolled fewer than five patients (10).

“Off-shoring of clinical trials. Increasing competition, growth of private practice oncology and other factors have impeded accrual to trials. Since cancer is many different diseases, each type with a relatively limited number of patients, it has become increasingly difficult to enroll sufficient numbers of patients in clinical trials in a reasonable time. Consequently, more centers

are needed, further increasing cost and complexity of conducting and monitoring clinical investigation.

A growing number of clinical trials are conducted outside the U.S. and there is increasing dependence on foreign data for approvals. Studies done in the late 1990s by the Tufts Center for Study of Drug Development showed that 15-20% of FDA regulated clinical trials were conducted outside the U.S. Recent data from Parexel, a large U.S. based commercial contract research organization, indicates that 41% of the clinical trial sites conducting FDA-regulated studies are from foreign countries based on analysis of Form 1572s (Table 2).

An intangible negative consequence of “off-shoring” of clinical research is the difficulty in ensuring quality of data, possible impact of genetic or racial differences on drug effects and the potential for obtaining misleading results due to differences in standards of care between geographic regions. One can anticipate that “off-shoring” of clinical research will increase with the emergence of both India and China as more cost-effective alternatives for conducting preclinical and clinical research and the opportunity for faster patient enrollment on clinical trials.

Fact or Fiction: The science of disease is more complex making it more challenging to develop drugs

Both the GAO and FDA reports argue that a growing difficulty in effectively translating basic research discoveries into new and effective medicines has contributed to increased failure rates during clinical testing (3,4). The volume of new drugs and *complexity of diseases to be addressed* have increased. New technologies including genomics, proteomics and nanotechnology have provided tools for researchers to discover and test compounds. However, the use of these technologies has led to increasing expenses without a commensurate increase in the number of drugs developed. Furthermore, according to the reports, a shortage of physician-scientists, also known as translational researchers, is seen as a fundamental barrier to increasing the productivity of drug development.

While these arguments may apply to the development of drugs for other diseases, it is unlikely that they are relevant to cancer drug development. There is no question that cancer is now better understood than it was years ago. Improvements in pathology, diagnostic imaging and other areas have

provided physicians with a better understanding of the disease and its natural history. Breakthroughs in molecular biology, pharmacology, immunology and biochemistry have produced a clearer picture of the pathogenesis of cancer and identified numerous attractive targets for drug development. These breakthroughs have spawned the emergence of the biotech industry and stimulated the participation of small entrepreneurial companies in drug discovery. The number of new cancer therapeutics entering clinical trials has been steadily increasing (Figure 1) consistent with this greater understanding, effort and focus on cancer.

Funding for cancer research and the number of trained Board certified oncologists have dramatically increased over the past few decades. Although stagnant over the past few years, the NCI budget doubled from roughly \$2 billion to \$4 billion in the 1990s and was almost \$6 billion in 2007. By 2005, the number of oncologists in the U.S. had more than doubled in two decades to about 13,000; of these, 81% were medical oncologists and 14% were pediatric oncologists (11).

It is, therefore, implausible to suggest that increasing disease complexity and lack of trained physicians are responsible for the slow-down in cancer drug discovery. One should expect that a better understanding of the science of cancer and its clinical behavior, and more trained specialists in oncology would lead to an acceleration of cancer drug development and improved efficiency of the drug discovery process.

The Regulatory System is Hampering Oncology Drug Development and Stifling Innovation

The numbers of new drugs in the pipelines of pharmaceutical companies is shrinking. Many factors are operating to stifle innovation including: higher FDA regulatory burdens, product liability concerns, fear of price controls, weakening of intellectual property laws and increased industry consolidation through mergers and acquisitions. I would like to address, what I consider to be the three most critical issues relating to FDA regulation.

One size-fits-all. Congressional and media attention surrounding drug safety problems (e.g. Fen-Phen in 1997, Propulsid and Rezulin in 2000, Baycol in 2001, Vioxx in 2005 and Avandia 2007) have heightened an already risk-averse behavior at FDA. This has made regulators more fearful and drives them to rely on 1) old established drug development paradigms, 2) act more

slowly on drug approvals and 3) require more pre-clinical and clinical testing. While these reactions may be acceptable for drugs intended to treat relatively benign conditions, where satisfactory alternative therapies exist, they are not appropriate when dealing with innovative products intended to treat deadly conditions.

Primarily in response to the AIDS epidemic, Congress understood the need for putting regulatory requirements in proper context by passing legislation, in the 1990s, designed to streamline the approval requirements for drugs intended to treat life-threatening diseases such as AIDS and cancer. FDA regulations emanating from this legislation resulted in a plethora of new drugs for AIDS and cancer utilizing regulatory procedures known as Fast-Track, Accelerated Approvals and others. Unfortunately, it appears that recent drug safety problems are having a chilling affect on the development and approval of oncology drugs.

A 2004 report completed for the European Union found that the withdrawals of the above noted drugs from the market affected FDA's implementation of regulatory standards (12). FDA began demanding more testing including 1) drug interactions, 2) effects on liver metabolism, 3) relationship to cardiac risk and 4) more lengthy and costly clinical trials.

As noted in the GAO report, increasing technical hurdles and cost have led industry leaders to abandon development of innovative drugs in favor of "me-to" drugs with less uncertainty.

One recent example is worth discussing. As a result of safety concerns noted above, all drugs now require evaluation both in *in vitro* preclinical and clinical tests for their potential affect on cardiac electrophysiology measured by their impact on the Q-T interval of the electrocardiogram. Many potentially useful drugs are abandoned because they score positively in an unreliable and poorly predictive assay. Potential drug effects on cardiac electrophysiology now must be evaluated in early clinical trials using cumbersome and expensive procedures that most authorities also believe are not predictive of toxicity. These tests are inconvenient for the patient requiring numerous electrocardiograms (ECG) and continuous cardiac monitoring to determine if the Q-T interval of the ECG is prolonged following administration of the drug. Many commonly used drugs, such as antibiotics, anti-emetics and sedatives, and diet may cause prolongation of the Q-T interval. While risk-benefit considerations may justify this testing

for some drugs, it is overly conservative to require this for drugs intended to treat life-threatening diseases where patients face certain death. In addition to cost, there are other unintended negative consequences of these testing requirements. Extensive and unnecessary cardiac monitoring is a serious impediment to patient recruitment in phase 1 clinical trials and forces very ill patients to undergo inconvenient tests.

Use of outdated clinical endpoints and statistical methods. According to the Critical Path Initiative report, “The medical product development process is no longer able to keep pace with basic scientific innovation.” This deficiency is no more striking than in the area of oncology where current clinical trial designs and endpoints are obsolete. Many of the more recently discovered oncology drugs possess mechanisms of action that defy use of standard oncology efficacy measurements such as tumor response. For example, cytostatic agents have now been developed that produce clinical benefit without measurable reduction of tumor size. Although, one such agent, Nexavar (sorafenib), has been approved, its approval was delayed for 1.5 years because regulators were not sufficiently convinced of its efficacy despite a randomized trial showing that patients maintained on the drug went statistically significantly longer before experiencing tumor progression compared to placebo. This drug is now widely used to treat renal cell cancer and hepatic cancer and it is being tested in other cancers.

In contrast to other areas of drug regulation and medicine, oncology drugs often require the need to demonstrate survival advantages. Eloxitan (oxaliplatin) is a drug that is now commonly used for the treatment of metastatic colorectal cancer, the third most common cause of death from cancer in the U.S. A New Drug Application for this drug was filed in February of 1999 with two large randomized trials showing that Eloxitan, when added to standard therapy, had clear anti-tumor activity based on improved tumor response and progression free survival. However, the NDA was not approved because the survival difference between the treatment arms, although superior for Eloxitan, was not statistically significant ($P=0.12$). The FDA required that the sponsor conduct another study, which delayed approval until the drug received accelerated approval—a *non-sequitur* in this case-- in August of 2002 (13).

Subsequent clinical studies have conclusively established that Eloxitan improves survival; that is, it saves lives. Unfortunately, for the

approximately 52,000 U.S. patients per year who die from metastatic colorectal cancer, it took an additional three years to get access to the drug.

The dependence on a survival endpoint places an unusual burden on cancer drug approval, which is not shared with other areas of medicine.

Genentech's blockbuster drug, Avastin (bevacizumab), approved in the United States for treatment of lung and colorectal cancer, went before the FDA's outside oncology drug advisory panel in December of 2007 for consideration of approval for treating metastatic breast cancer. In a large clinical trial, Avastin added to standard therapy, was found to double the time to tumor progression and more than twice as many patients had significant tumor shrinkage. The progression free survival in the Avastin arm was superior to any previously reported metastatic breast cancer study. Avastin-treated patients also survived slightly longer, but not to a statistically significant level (14).

The clinical findings were felt to be of such immediate importance that they were presented in 2005 at the Annual Meeting of the American Society of Clinical Oncology, as a "late-breaking" abstract. Late-breaking abstracts are reserved for clinical study findings that are "clinical practice changing." The data were met with extreme enthusiasm by physicians who began using the drug "off-label" to treat patients with breast cancer.

Still, despite Avastin's widespread acceptance by many oncologists, FDA continues to press for survival advantages, so the FDA panel of outside advisors voted 5-4 against approval. In February 2008, FDA granted accelerated approval for Avastin, a surprising and contorted use of this regulation, which requires the sponsor to conduct additional clinical studies before it can gain standard approval.

As sadly demonstrated with Avastin for breast cancer, FDA needs to streamline its approval process for cancer drugs, and stop requiring now outdated problematic endpoints such as survival -- where confounding factors, such as other therapies delivered after the study treatment, confuse the test drug effect. Due to our progress against cancer and the availability of additional active agents, for many types of cancer it is no longer possible to use survival as the endpoint.

Statistical procedures required by FDA are outdated and may produce confusing or inaccurate results that are putting patients at risk. Inflexible

dependence on single pre-specified endpoints and use of procedures which fail to account for baseline covariates may lead to misleading results, which are discouraging clinical investigation in areas of oncology where patient heterogeneity is substantial and poorly understood. Use of analyses relying on average effects, such as the Kaplan-Meier analysis, do not capture critical information that may inform proper treatment choices for specific patients as recently suggested by Kent and Hayward who advocate a risk-adjusted analysis (15,16).

In the era of genomics and hope for personalized medicine, use of newer statistical procedures will be required. Genome wide sequencing has shown that individuals and their tumors vary considerably. Relying on a single pre-defined endpoint, based on average effects, neglects the opportunities to uncover valuable information embedded in sub-groups within large clinical trials. Frequently, these sub-groups are apparent only after enrollment of the trial is completed. This is appreciated by FDA in the Critical Path Initiative where novel clinical trial design, statistics, use of biomarkers and other ideas are encouraged. However, without enlightened cooperation between FDA and industry, these ideas may never be implemented. Even though superior to current standard methods, industry will be hesitant to use novel statistical methods without encouragement and flexibility from FDA.

Regression of accelerated approval. Accelerated approval gave desperately needy patients faster access to new drugs. It allows for conditional approval based on data "reasonably likely" to predict clinical benefit while lengthy more definitive trials are conducted. The idea worked: 26 new cancer drugs for 30 different clinical indications were approved between 1995 and 2005 under the accelerated approval regulation. Important drugs such as Camptosar, Eloxitan, Gleevec, Temodar and others were made available to patients more quickly than would have been the case under the standard approval procedures (17,18). Thousands of patients benefited from faster access, and these drugs went on to find vital and expanded roles for the treatment of many types of cancer. There appears to be no evidence that any harm was done by accelerating the approval process for these products. Indirectly, the streamlined review and approval process also stimulated the pharmaceutical industry to invest in the development of new drugs for these difficult diseases.

In recent years, the FDA has effectively regressed to a pre-AIDS mindset. The accelerated approval requirements have stiffened and the real benefits of

the process for patients have been whittled away. The first step backward was requiring that sponsors submit a protocol for the planned confirmatory trial before conditional approval could be granted. Then came a requirement that patient enrollment must first be initiated in the confirmatory trial, then a requirement that all patients be fully enrolled in the trial. Most recently, the FDA has decided it would prefer to wait for the final data from the confirmatory trial before granting "accelerated approval," making a mockery of the term and effectively killing the whole concept behind it.

An illustrative example is that of pancreatic cancer. Only two drugs have ever been approved to treat pancreatic cancer, and only one new drug has been approved in the last 11 years. Yet it is one of the most lethal forms of cancer and the nation's fourth most common cause of cancer death. This year, 37,000 Americans will be diagnosed, and three-fourths of them will die from the disease within 12 months of their diagnosis. Only 5% are alive at five years.

In 1996, the FDA approved Gemzar (gemcitabine) to treat pancreatic cancer. Lilly, the manufacturer of Gemzar, embarked on a phase 3 randomized trial with concurrence from FDA that they could receive accelerated approval by using improvement in disease-related symptoms such as pain, performance of daily activities and weight change as an endpoint for the trial. Earlier studies with the drug did not produce the usual tumor response data or show any impact on survival but had shown a reduction in pain and disease related symptoms. This phase 3 study was motivated by FDA's allowance of the use of this novel endpoint, rather than survival. Further experience and research with this drug demonstrated that it prolonged survival of patients with pancreatic cancer, and it has gone on to find a valuable role in treating other cancers, including lung, ovary and breast cancers.

Since 1996 progress against pancreatic cancer has stalled. In 2007, Tarceva (erlotinib) was approved for pancreatic cancer using a traditional survival endpoint. Tarceva plus Gemzar received an approval based on a median survival difference of only 9 days compared to Gemzar alone; a poignant demonstration of the absurdity of statistical significance in the face of questionable clinical benefit (19).

According to the National Institutes of Health's clinical trial database, the number of later-stage clinical trials for pancreatic cancer currently under way is a fraction of those being conducted for other, comparable diseases

like breast, lung, prostate and colorectal cancers. The pessimism has spread to physicians: A recent study showed that more than 30% of patients with operable, localized pancreatic cancer were not offered potentially curative surgery because of fatalistic and cynical views held by their doctors (20).

To crack through this pessimism, we need to kick-start a new era of intense, focused collaboration between government, business and academia. For starters, the FDA should utilize the Accelerated Approval regulations as they were originally intended when they came into effect in 1992. This will allow for conditional approval of promising drugs based on the use of surrogate endpoints, which are endpoints requiring shorter-term patient follow-up but are reasonably likely to predict clinical benefit.

Reflections on the past and looking to the future

The war on cancer stimulated breakthroughs in science and medicine that led to the creation of dozens of new cancer products that have improved the prognosis for many patients with cancer. Diagnostic imaging, *in vitro* diagnostics and better drugs have led to earlier diagnosis and better outcomes. In the 1960s and 1970s there were few cancer drugs, they had limited applications and were associated with serious side effects. The explosion of new therapies in the 1990s resulted from the 1971 war on cancer legislation, with approximately a twenty year lag given the time it takes to discover and develop new drugs (Figure 2). Most likely, the expedited drug approval regulations promulgated in the late 1980s and early 1990s further contributed to the increase in drug approvals. Among these regulations, Accelerated Approval was a great success with twenty six new drugs, most of them of substantial importance, entering the market and becoming available to physicians and their patients with cancer.

Recently, however, a risk-averse regulatory mentality, which potentially warranted for certain indications, has spread into the oncology area and appears to be exerting a strong negative influence on discovery and innovation. Unfortunately, it will be difficult to assess the immediate impact of the additional requirements that FDA and other regulatory bodies (e.g. institutional review boards, grants and contract offices) have imposed on drug development and approval. At first glance, many of the individual requirements appear to add minimal burden to development of drugs, but collectively they place almost insurmountable obstacles to successful drug discovery, preclinical and clinical testing and approval.

It will take decades before we can evaluate the true impact of these increasing regulatory demands and risk-averse behavior on product innovation. In the meantime, there is a clear and present danger for patients with life-threatening diseases. It is not surprising, therefore, that various patient groups (e.g. Abigail Alliance) have become more aggressive in their struggles to obtain promising but experimental new treatments prior to FDA approvals (21). One can anticipate that these movements will increase along with a growing distrust of our regulatory and clinical trial enterprise. The past few decades have taught us that flexible and rational regulatory policy, availability of funding resources and concerted efforts from government, academia and industry could successfully affect a complex and deadly group of diseases such as cancer.

The FDA's Critical Path Initiative outlines a need to make fundamental changes to the drug discovery and approval paradigm in order to continue to make progress against killer diseases. The Critical Path Initiative correctly identifies the need to modernize the drug development and approval process and to implement newly discovered scientific tools in this process e.g. genomics, biomarkers, adaptive clinical trial designs, etc. Unfortunately, as documented in the recent report, "FDA Science and Mission at Risk," by the Subcommittee on Science and Technology, "the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities (22)."

How will new drugs be discovered and developed if novel inventions must be twisted and forced to fit the use of outdated, but acceptable regulatory procedures? What drug company leaders will be courageous or committed enough to utilize procedures noted in the Critical Path Initiative in a risk-averse environment and with an Agency that appears to lack the scientific capacity to understand or evaluate the approaches? And who will put these risks and rewards in proper perspective for patients and their doctors and be willing to make the choices? Science, medicine and biostatistics together with clinical judgment, compassion for patients and a proper sense of urgency should replace bureaucracy, which although satisfying the needs for some, is not addressing the needs of critically ill patients.

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Table 1. Regulatory Characteristics of Oncology Drugs

Characteristic	%	
	Oncology	Other
Priority*	70.9	40.2
Orphan Drug	48.5	18.5
Expedited Access**	47.1	13.4

* FDA action within 6 months of NDA filing
** Accelerated approval, sub-part E or Fast Track

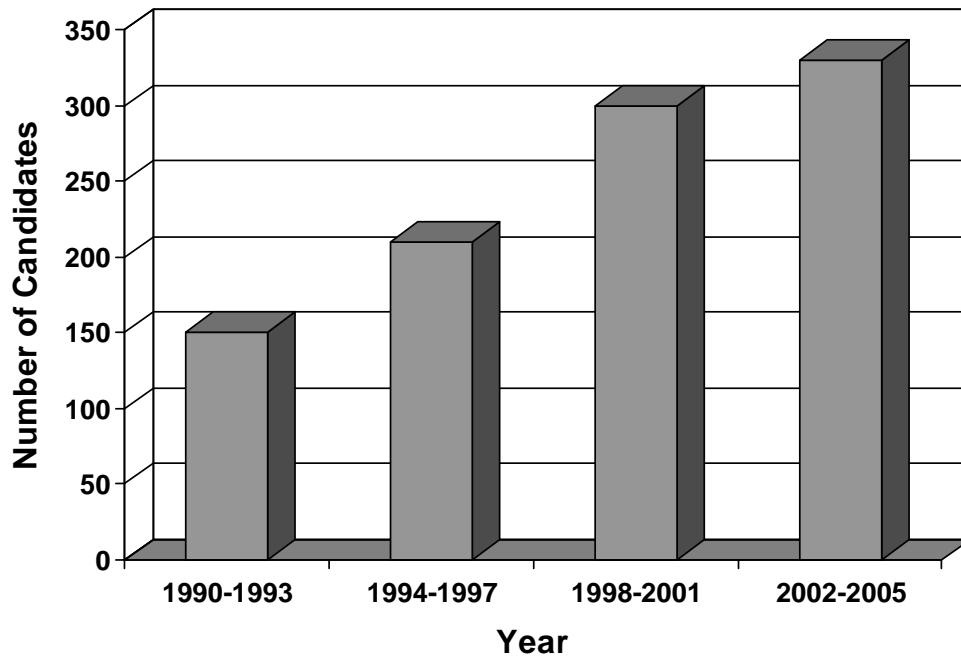
Table 2. Number of Investigators Completing 1572s to Participate in FDA-Regulated Clinical Studies in 2006: Top 13 Countries
(clinical investigators completing Form 1572s in 2006)

	Number of Investigators	% of Total
United States	13,629	59%
Canada	893	3.9%
France	600	2.6%
Germany	583	2.5%
Spain	576	2.5%
United Kingdom	462	2.0%
Russia	443	1.9%
Italy	389	1.7%
Argentina	358	1.6%
India	306	1.3%
Australia	287	1.2%
Poland	276	1.2%
South Africa	232	1.0%

Source: PAREXEL's Bio/Pharmaceutical R&D Statistical Sourcebook 2007/2008; BMIS

Figure 1.

New Cancer Therapeutics Entering Clinical Trials



Source: Tufts CSDD, 9:Sept/Oct '07

Figure 2.

Approved New Molecules for Cancer

