Economics of Cancer Drug Development

By Michael Dickson, PhD, and Gene Reeder, PhD

ABSTRACT

Cancer is among the three top causes of death in the United States, with an annual cost of disease approaching $200 million. Research into pharmaceutical treatments for cancer are becoming more targeted to molecular sites based on the emerging discipline of pharmacogenomics. While this approach offers promise for improvements in the safety and efficacy of cancer treatment, the economic environment that influences pharmaceutical research presents conflicting signals. Because pharmacogenomic based therapies will be more site-specific, the sales potential for a given product will diminish which ultimately reduces the revenue base from which pharmaceutical research is funded. Research-based pharmaceutical companies are likely to respond by increasing efficiency clinical in drug development and clinical trials, integration of pharmaceuticals with related products (eg, diagnostics and testing), and expansion of market possibilities through continued globalization. Pharmacogenomics holds great promise for developing highly specific cancer therapies, but the economic realities of drug development present an uncertain pathway to the desired outcome.

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INTRODUCTION

The three most common causes of death in the United States and other developed countries are heart disease, cancer, and stroke.[1] In the US alone, the overall cost of cancer was estimated to be $180.2 billion ($60 billion in direct medical costs) in 2000.[2] Therefore, it is no surprise that considerable public and private funds are devoted to developing cancer treatments. In 2001, the National Institutes of Health's budget for cancer research was $4.4 billion.[2*] This amount does not include private funding for cancer research or the pharmaceutical industry's investment.

Pharmaceuticals are an important part of the research effort, and no fewer than 400 new agents are currently under development by US-based pharmaceutical companies. The route for any new innovative drug from the laboratory to the patient is long and costly. It takes an estimated 12–5 years and $250–500 million, on average, for a new chemical entity to obtain marketing approval.[4,5] While some observers regard the resources devoted to cancer research in general, and pharmaceutical research in particular, as inadequate, they cannot be labeled trivial and there has been progress on many fronts.

For all the reasons cited above, as well as the desire to ameliorate the personal tragedy of cancer, there is keen interest in reducing both the time and the cost of developing more effective and less toxic cancer drug therapies (for a review, see Evans and Relling).[6] In the last 3 years, the professional literature has provided a steady stream of information about the field of pharmacogenomics, which some regard as the most promising approach to developing new drugs, whether for cancer or other diseases. Pharmacogenomics is sometimes used to mean molecular drug targeting—creating drug treatments that have a high degree of specificity for a molecularly defined site of action.

This article reviews the special economic dimensions of cancer drug development, and especially examines the potential role of pharmacogenomics in improving the safety, efficacy, and economics of cancer drugs. Because the economics of drug development cannot be divorced from the traditional considerations of safety and efficacy, these issues will be explored as they relate to the economic perspective. Whether the appropriate level of funding for cancer research has been achieved is a political question and therefore is not addressed.

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Pharmacogenomics presents the possibility of developing much more specific cancer treatments which are expected to decrease adverse effects, increase efficacy, and improve outcomes.

New cancer therapies based on pharmacogenomic principles are likely to expand pharmacist responsibilities for patient care because they will require the integration of pharmacy related services (diagnostic and testing) with drug therapy.

Formulary committees will be expected to place pharmacogenomics on the formulary, and develop methods for insuring appropriate use with the objective of maximizing benefits within a budget.

Pharmacogenomics-based cancer treatment will expand the role of cancer nurses in the area of integration of care because cancer pharmacotherapy will be highly specific and require complex treatment regimens.

**For a critical view of the level of funding for cancer research, see the National Coalition for Cancer Research's Web site: www.cancercoalition.org.*

Dr. Dickson is professor of pharmacy and chairman of the Department of Pharmaceutical and Health Outcomes Sciences at the College of Pharmacy at the University of South Carolina in Columbia. Dr. Reeder is professor of pharmacy at the College of Pharmacy at the University of South Carolina.

THE GENERAL PROBLEM

For a pharmaceutical product to remain available to patients, it must be economically feasible in addition to being safe and effective.[†] Efficacy is essential to obtain marketing authorization for a product, but effectiveness must be demonstrated if a product is to gain acceptance by clinicians as a useful treatment for cancer. Consequently, the discovery and development of innovative new drugs is considered to be a risky economic venture because all elements of the development process and the competitive environment are either constantly changing or filled with uncertainty. For example, there are established models of how drugs and receptors interact, but lack of a complete biologic understanding introduces many unknowns. Similarly, the competitive environment is constantly changing and not always transparent. Therefore, business decisions are generally made using incomplete data, which only adds to the uncertain environment. Methods of drug development that reduce clinical and economic uncertainty will be embraced by drug developers.

Proponents of pharmacogenomics argue that this new technology will fill in some of the missing biologic gaps and thereby help to reduce toxicity and increase effectiveness of cancer drugs. There also are claims that pharmacogenomic technology will improve the economics of drug development, but that seems much less certain than the scientific possibilities. Thus, the business environment continues to be largely an unknown. If pharmacogenomic principles are as effective as many experts believe, we can expect significant clinical advances in cancer treatment. The unknowns are how long it will take for the benefits of pharmacogenomic technology to be realized and how it will affect the economics of new drug development. The latter question is significant because discovery and marketing of pharmaceuticals remain a private business enterprise that responds to market forces.

An appreciation of possible economic consequences of cancer drug development requires consideration of four elements in the drug discovery and drug use process. Although we will initially discuss them separately, their interrelationships must also be considered. These elements and their interactions may change in the future, but the process is now based on the current scientific and business environment with a set of expectations about what the future will bring. The four factors most likely to influence the economics of cancer drug development are pharmacogenomics, healthcare market integration, globalization of the pharmaceutical market, and the new social contract for pharmaceuticals.

PHARMACOGENOMICS

The basic strategy for applying pharmacogenomics is that response to a drug varies, in part, because of genetic differences among those using the drug. This explains, to some degree, variations in efficacy and toxicity for a drug used to treat the same disease. If the genetic source of these differences can be identified, it can exploited to "match" a drug to a specific genetic type—thus enhancing efficacy and reducing safety problems. Veenstra and colleagues have described three mechanisms by which genetic variations can affect safety and efficacy: drug targets (receptors); drug transport mechanisms; and drug-metabolizing enzymes.[7] They argue that the cost-effectiveness of pharmacogenomic-based drugs will differ depending on which of these area is affected. The benefits of pharmacogenomic principles for safety and efficacy are obvious, but the economic consequences are more complex and less clear. For example, if a variant (disease-causing) gene occurs at a very low rate, the economics for drug development will be different from a very common variant because the potential for sales affects many economic dimensions.

The expectation is that enhanced specificity of pharmacotherapy based on pharmacogenomic principles will result in a reduced rate of toxicity and increased efficacy. It follows that there should be savings for the healthcare system since the costs of treating these unintended consequences can be substantial (eg, the costs of treating increased morbidity and mortality). Improved outcomes also are expected because of the drug's specificity for its intended population. However, these savings are unlikely to mean increased revenues for pharmaceutical companies. On the contrary, there is a strong likelihood that drug sales revenue will be reduced because a new drug will be targeted to a specific genetic population that is surely smaller than the general population of previous users. For example, the current generation of vitamin K inhibitors are not genetically specific, which requires that the dosage be individualized for each patient. If a genetically specific drug were developed, its users would be a subset of the current population with the disease. Those patients using the more specific drug would undoubtedly be better served by it (eg, reduced monitoring costs, fewer adverse effects, better control of coagulation, etc), but sales volume and dollars would almost certainly be lower than for a product based on current vitamin K inhibitor technology.

The reduced revenue that is likely to be seen with more specific agents could be offset, to some degree, by increased efficiency in the conduct of clinical trials. Currently, clinical trials do not commonly include genetic screening as part of the patient selection process. In the future, selection criteria are likely to include a genetic screen so that only those patients with a genetic profile specific for the drug will be included in a trial. Genetic screening will reduce the incidence and severity of adverse events, and participants will have an enhanced possibility of responding to the experimental drug. The net result is that clinical trials will become more efficient.

[†] *It is important to distinguish between efficacy and effectiveness. Efficacy is the ability to achieve the expected result in a controlled clinical trial. Effectiveness is the degree to which a product can achieve the expected result in normal clinical practice (after marketing approval is received).*

Another economic benefit touted for pharmacogenomic-based drug development is that it will reduce costs by eliminating unpromising compounds earlier in the drug development process. With better information about molecular targets, compounds that lack the necessary specificity for the desired site can be quickly eliminated from further testing. Such compounds will, most likely, never get past Phase I of the clinical trial process. Since the most expensive part of drug testing occurs in Phases II and III, there can be considerable economic gains by early termination of unpromising compounds. Currently, a compound's specificity can only be inferred after Phase II and III clinical trials. This leaves unanswered questions about the costs of developing and applying pharmacogenomic principles to obtain compounds that are targeted to particular molecular sites.

A negative consequence of this more selective approach to drug development is that information about a new drug's usefulness in the general population (not just those who pass a genetic screen) will not be obtained because only a very select and homogeneous group will be admitted to the trial. This information could be obtained from a separate trial in which subjects are not genetically screened; however, this would be expensive and it runs counter to the principles of pharmacogenomic drug development.

If a compound is developed for a genetically specific group, there is no guarantee that its use after marketing approval will be restricted to only that type of patient. To the contrary, there are many reasons to believe that "off-label" use (eg, use of the drug for indications other than those for which it received marketing approval) is certain to occur once the new pharmacogenomically guided compound is approved for marketing.

Specifically, the drug will be used in patients who do not meet the particular genetic profile for which it was tested in clinical trials. And, since there were no trials in the general population, its effectiveness will be uncertain. Off-label use is common today because of limitations in the current drug development model and normal variations in clinical practice. Off-label use is sure to occur for pharmacogenomic cancer drugs because cancer patients often have few other options and the consequences of untreated disease are severe if not fatal. Even though we are entering a new era of high technology drug development, the complexities of cancer will remain beyond the immediate scope of available treatment options. Economically, off-label use will have a mixed result. From a strict cost-effectiveness perspective, results in the general population are certain to be lower than in the genetically homogeneous group for which the drug was approved. However, from the drug developer's perspective, there is a much larger base over which to amortize the costs of drug development.

As mentioned, a possible downside to pharmacogenomic-based drug development may be that a compound with some clinical potential will be stopped early in the development process because it is unlikely to be economically feasible. Yet, another view suggests that the compound should be pursued because it may be economically feasible in a niche market—ie, an orphan drug.

Development of orphan drugs is encouraged through tax incentives that make it economically attractive for pharmaceutical companies to develop drugs for very small disease markets. If this principle is to be applied to pharmacogenomic drugs, the definition of an orphan drug will have to be changed.[‡] Regulatory changes are driven by political considerations with uncertain time frames and outcomes. Experience with the current orphan drug law suggests that change will not be easy. The prospect for development of economically feasible niche markets in the short-term is limited, but we should not discount the ability of disease advocacy groups to change the political environment in the medium to long term. Regardless of the time frame, a change in the definition of an orphan drug to include pharmacogenomic-based products will require valid, reliable, and economically feasible diagnostic tests to identify subjects.

HEALTHCARE MARKET INTEGRATION

Diagnostic testing is the enabling technology for the efficient use of pharmacogenomic drugs and, therefore, the key to their economic success. Economics dictates and previous experience suggests that not all patients will need drugs with the specificity of pharmacogenomic-based drugs. Because pharmacogenomic drugs will be expensive, it will not be efficient to use them in all cases. This situation is amplified many-fold for cancer drugs because of the consequences of treatment failure and the emotional content of the therapeutic category. The key economic question is when to use a genetically specific drug. This is not unlike the current environment in which the decision to use a drug is based on incomplete information. For example, should a patient be treated prophylactically to prevent a condition that may not develop? If we do treat the patient, what is the likelihood that the outcome will be favorable? As the cost and consequences of treatment rise, the economic and clinical stakes increase.

Diagnostic tests are not only essential to the success of developing drugs based on pharmacogenomic principles, they also are essential for making the products of this process economically viable. From the perspective of pharmaceutical companies, this is an opportunity to integrate the diagnostic and testing market with appropriate pharmaceutical markets. While this occurs in the current market (eg, diabetes testing linked with products for diabetes treatment), linkage will be necessary for commercial success of genetically specific pharmaceuticals since the latter will, by definition, have a limited population of patients. Clinical success of the products also depends on availability of diagnostic tests to identify appropriate patients and to

[‡] *Currently an orphan drug (in the US) treats a disease that has a prevalence of less than 250,000 cases. The condition may be caused by genetic mutations, but orphan drug status is not defined in genetic terms.*

monitor treatment. Thus, the economics of drug development depend not only on the activities in the premarketing phase of drug development, but also on conditions in the market when the drug becomes available. This is true today also, but the conditions are less essential for economic viability of a product today than they will be in the future.

Managed care organizations (MCOs) have driven much of the trend toward integration in the pharmaceutical industry. For example, research-oriented pharmaceutical companies have formed alliances (or purchased) generic companies in an effort to offer drug therapies across the economic spectrum for their MCO customers. Companies also have integrated with nonpharmaceutical businesses to provide comprehensive disease management programs for their clients (eg, counseling services and psychotherapeutic agents for mental health management programs). Pharmacogenomics is likely to add at least two other components to this integration strategy because diagnostic testing will be an essential part of using pharmaceuticals developed based on these strategies. MCOs will be keen to insure that a therapy is clinically appropriate and the best choice economically. This is the basis for expansion of the generic market and there is every reason to expect that this same economic philosophy will be applied to cancer treatment. Specifically, payers will attempt to identify and pay for the least costly effective treatment for a patient.

If the cost of drug development continues to rise, as everyone expects, and if there continues to be resistance to the cost of pharmacotherapy by payers and patients, then it will be necessary to spread the cost of drug development over many users. One approach that drug developers can use to amortize the cost of drug development is market integration. Expanding the patient base is another possibility.

GLOBALIZATION OF THE PHARMACEUTICAL MARKET

Globalization of the pharmaceutical market is synergistic with pharmacogenomics and integration in healthcare markets because it helps to expand the base over which to amortize the development costs for new drugs. Access to larger populations will increase the efficiency described above as well as the genetic diversity available for drug development. In addition to improved efficiency through increased numbers and varieties of patients, globalization of pharmaceutical markets promotes more rapid access to important new cancer therapies. The International Commission on Harmonization (ICH) continues to work for harmonization of drug approval procedures with the expectation that it will ultimately reduce both the cost of drug development and the time required to gain market access.[§]

The second factor in globalization of the pharmaceutical market that will influence the economics of drug development is the disparity in prices across countries. It is generally acknowledged that pharmaceutical prices among developed countries are higher in the US than in other countries.[8] If European- or Canadian-style price and utilization constraints are introduced in the US, there could be an adverse effect on research investment among US-based research-oriented pharmaceutical companies. Recent developments in several countries increase the possibility of some type of price constraints in the US, although this is not a certainty.

THE NEW SOCIAL CONTRACT ON PHARMACEUTICALS

As Americans we spend about 13.5% of our gross domestic product on health care, and about 10% of this is for pharmaceuticals.[9] Our total and per capita expenditure for health is higher than any other country, but expenditure for pharmaceuticals as a percentage of total health expenditure is often higher in other countries.[10] Although pharmaceuticals are a small part of the total in comparison with other countries, the economic burden falls unevenly amongst the various economic brackets within the US population. There is a growing expectation that something must be done to make pharmaceutical treatments more affordable; at least for that part of the population most in need and least able to pay.[11] Pharmaceutical firms have found themselves in a defensive posture on this issue and the current Medicare debate will do nothing to move the spotlight. The issue of prices for AIDS drugs in developing countries is yet another manifestation of the current view that pharmaceuticals (at least some of them) should be available at little or no cost if patients cannot pay. This new public attitude toward the pharmaceutical industry has implications for the economics of drug development. Although the US-based research-oriented pharmaceutical industry currently invests 17% of sales revenue which is estimated to be $165 for the year 2000 in research,[12] some say this research spending goes to less important priorities.

Critics are increasingly stating that pharmaceutical companies should direct their research efforts and resources toward solving significant health problems (eg, heart disease, cancer, and stroke) rather than devoting resources to less clinically important areas, such as modifications to existing products or the development of "lifestyle" drugs. However, it must be said that this is a complex issue with opposing points of view. Defenders of the pharmaceutical industry note that the resources needed to invest in long-term, high-risk research necessary for solving the more difficult, but clinically important, problems must come from some of the products most castigated by critics. They further state that a more realistic view of research recognizes that advancements in pharmaceutical therapy are more often incremental than revolutionary. Thus, there is an expectation of balance between the two

[§] *The ICH was created by pharmaceutical regulatory agencies and pharmaceutical company trade associations in the US, the European Union, and Japan. The ICH also has associate members from other countries with large pharmaceutical markets. For information on the ICH mission and accomplishments, a convenient site is www.ifpma.org.*

positions. This dynamic tension has clear implications for the development of new innovative cancer drugs. If the pendulum were to swing too far in either direction, the current balance could change. Whether the current balance is appropriate depends on one's perspective; however, it is clear that both points of view have validity and must be addressed.

The general public and payers have internalized this view in their attitudes toward the cost of prescriptions. Insurers, in particular, are scrutinizing new products more carefully and attempting to compensate companies based on value rather than uniqueness of a compound. Some payers are linking reimbursement levels across a group of products rather than considering each separately. Inherent in this message is that research is expected to target solutions for socially significant problems. By inference, cancer should be among the areas to receive a high degree of research effort.

INTERRELATIONSHIPS

The economic issues in molecular drug targeting (pharmacogenomics) are intimately connected to other topics addressed here. The forces are by no means equal for each component and the mix is unstable. However, any discussion of the new drug development environment would not be complete without some description of how the previous points interact with each other and the current drug development environment.

Movement away from the current drug development environment to a system based on pharmacogenomic principles will occur to the extent that it is economically feasible. There is ample evidence to suggest that the technology can improve the quality of the drugs produced, but it is not clear that it is economically feasible. More correctly, the extent of the shift from "traditional" drug development methods to a pharmacogenomic system is not clear. Where does it make sense to use the new technology and where is it better to use less expensive strategies? The answers depend on the interaction among the pieces described above.

As noted, availability of rapid, relatively inexpensive, valid, and reliable genetic testing is essential. If this technology is slow to develop, then changes in drug development methods will be slow as well. We should not be surprised that, regardless of the speed with which technological developments occur, the first benefits will come from the "low hanging fruit," ie, not necessarily the areas of greatest need. This results from the economic conditions necessary for advancing technology.

The nontechnological issues (market integration, globalization, and societal views) will help to determine the economic environment and define the incentive structure for the pharmaceutical industry. Governments can influence the economic environment through regulations that encourage or constrain research, but few if any governments are actively engaged in the drug development process. But, as described, the economic feasibility of a new drug can be determined by tax incentives that are expected to provide direction for drug development.

The current trend toward market globalization will impact new drug development, especially in the US because of the heavy investment in biotechnology. If the economic or scientific incentive structure becomes less favorable, it could change the focus of new drug development. The benefit of drug development is increasingly viewed as a social good to which there should be equity in access. This view may be unique among private industries that produce products for public consumption.

CONCLUSIONS

Economic forces at work to influence the economics of drug development have been reviewed. The technology on which molecular targeting for new drugs will be based has been described in general terms to provide a perspective from which to consider the economics of new drug development. We can expect that the future productivity of the drug development enterprise will be determined as much by the economics of pharmaceutical use as by the technology. **OS**

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