11 Economic Considerations in Medical Biotechnology

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INTRODUCTION

The biotechnology revolution has coincided with another revolution in health care: the emergence of finance and economics as major issues in the use and success of new medical technologies. Health care finance has become a major social issue in nearly every nation, and the evaluation and scrutiny of the pricing and value of new treatments has become an industry unto itself. The most tangible effect of this change is the establishment of the so-called third hurdle for approval of new agents in many nations, after proving safety and efficacy. Beyond the traditional requirements for demonstrating the efficacy and safety of new agents, some nations and many private health care systems now demand data on the economic costs and benefits of new medicines. Although currently required only in a few countries, methods to extend similar prerequisites are being examined by the governments of most developed nations. Many managed care organizations in the USA now prefer that an economic dossier be submitted along with the clinical dossier to make formulary coverage decisions.

The licensing of new agents in most non-US nations has traditionally been accompanied by a parallel process of price and reimbursement approval, and the development of an economic dossier has emerged as a means of securing the highest possible rates of reimbursement. In recent years, sets of economic guidelines have been developed and adopted by the regulatory authorities of several nations to assist them in their decisions to reimburse new products. As many of the products of biotechnology are used to treat costly disorders and the products themselves are often costly to discover and produce, these new agents have presented new problems to those charged with the financing of medical care delivery. The movement to require an economic rationale for the pricing of new agents brings new challenges to those developing such agents. These requirements also provide firms with new tools to help determine which new technologies will provide the most value to society as well as contribute the greatest financial returns to those developing and marketing the products.

THE VALUE OF A NEW MEDICAL TECHNOLOGY

The task of determining the value of a new agent should fall somewhere within the purview of the marketing function of a firm. Although some companies have established health care economic capabilities within the clinical research structure of their organizations, it is essential that the group that addresses the value of a new product does so from the perspective of the market and not of the company or the research team. This is important for two reasons. First, evaluating the product candidate from the perspective of the user, and not from the team that is developing it, can minimize the bias that is inherent in evaluating one's own creations. Second, and most importantly, a market focus will move the evaluation away from the technical and scientifically interesting aspects of the product under evaluation and toward the real utility the product might bring to the medical care marketplace. Although the scientific, or purely clinical, aspects of a new product should never be ignored, when the time comes to measure the economic contribution of a new agent, those developing the new agent must move past these considerations. It is the tangible effects that a new treatment will have on the patient and the health care system that determine its value, not the technology supporting it. The phrase to keep in mind is "value in use."

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The importance of a marketing focus when evaluating the economic effects of a new agent, or product candidate, cannot be overstated. Failing to consider the product's value in use can result in overly optimistic expectations of sales performance and market acceptance. Marketing is often defined as the process of identifying and filling the needs of the market. If this is the case, then the developers of new pharmaceutical technologies must ask two questions: "What does the market need?" and "What does the market want?" Analysis of the pharmaceutical market in the first decade of the twenty-first century will show that the market needs and wants:

- Lower costs
- Controllable costs
- Predictable cost
- Improved outcomes

Note that this list does not include new therapeutic agents. From the perspective of many payers, authorities, clinicians, and buyers, a new agent, in and of itself, is a challenge. The effort required to evaluate a new agent and prepare recommendations to adopt or reject it takes time away from other efforts. For many in the health care delivery system, a new drug means more work—not that they are opposed to innovation, but newness in and of itself, regardless of the technology behind it, has no intrinsic value. The value of new technologies is in their efficiency and their ability to render results that are not available through other methods or at costs significantly lower than other interventions. Documenting and understanding the economic effects of new technologies on the various health care systems help the firm to allocate its resources more appropriately, accelerate the adoption of new technologies into the health care system, and reap the financial rewards of its innovation.

There are many different aspects of the term "value," depending upon the perspective of the individual or group evaluating a new product and the needs that are met by the product itself. When developing new medical technologies, it is useful to look to the market to determine the aspects of a product that could create and capture the greatest amount of value. Two products that have entered the market provide good examples of the different ways in which value is assessed.

Activase® (tPA, tissue plasminogen activator) from Genentech, one of the first biotechnology entrants in health care, entered the market priced at nearly ten times the price level of streptokinase, its nearest competitor. This product, which is used solely in the hospital setting, significantly increased the cost of medical treatment of patients suffering myocardial infarctions. But the problems associated with streptokinase and the great urgency of need for treatments for acute infarctions were such that many cardiologists believed that any product that proved useful in this area would be worth the added cost. The hospitals, which in the USA are reimbursed on a capitated basis for the bulk of such procedures, were essentially forced to subsidize the use of the agent, as they were unable to pass the added cost of tPA to many of their patients' insurers. The pricing of the product created a significant controversy, but the sales of Activase and its successors have been growing consistently since its launch. The key driver of value for tPA has been, and continues to be, the urgency of the underlying condition. The ability of the product to reduce the rate of immediate mortality is what drives its value. Once the product became a standard of care, incidentally, reimbursement rates were increased to accommodate it, making its economic value positive to hospitals.

An early biotechnology product that delivered a different type of value is the granulocyte-colony stimulating factor Neupogen® from Amgen, which was priced well below its economic value. The product's primary benefit is in the reduction of serious infections in cancer patients, who often suffer significant decreases in white blood cells due to chemotherapy. By bolstering the white blood cell count, Neupogen allows oncologists to use more efficacious doses of cytotoxic oncology agents while decreasing the rate of infection and subsequent hospitalization for cancer patients. It has been estimated that the use of Neupogen reduces the expected cost of treating infections by roughly $6000 U.S. per cancer patient per course of therapy. At a price of roughly $1400 per course of therapy, Neupogen not only provides better clinical care but also offers savings of approximately $4600 U.S. per patient. The economic benefits of the product have helped it to gain use rapidly with significantly fewer restrictions than products such as tPA, whose economic value is not as readily apparent.

These two very successful products both provide clear clinical benefits, but their sources of value are quite different. The value of a new product may come from several sources, depending on the needs of clinicians and their perceptions of the situations in which they treat patients. Value can come from the enhancement of the positive aspects of treatment as well. A product that has a higher rate of efficacy than current therapies is the most obvious example of such a case. But any product that provides benefits in an area of critical need, where few or no current treatments are available, will be seen as providing immediate value. This was, and remains, the case for tPA.

Some current treatments bring risk, either because of the uncertainty of their effects on the patient (positive or negative) or because of the effort or cost required to use or understand the treatments. A new product that

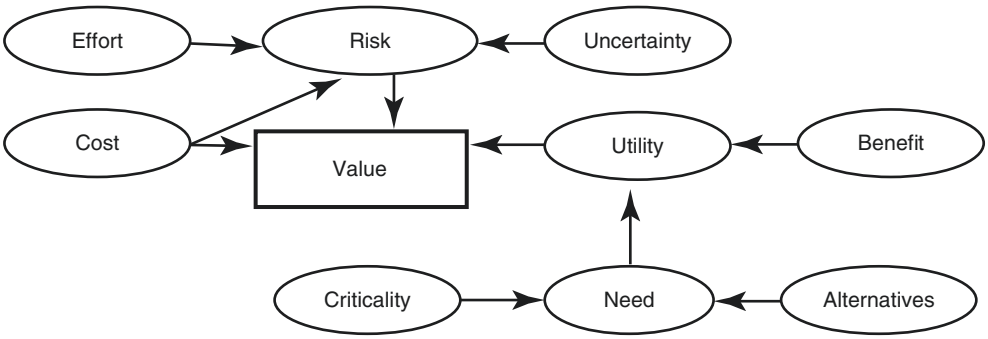

Figure 11.1 ■ Generalized model of value (Copyright © 2003, Medical Marketing Economics, LLC, Oxford, MS)

reduces this risk will be perceived as bringing new value to the market. In such cases, the new product removes or reduces some negative aspects of treatment. Neupogen, by reducing the chance of infection and reducing the average cost of treatment, brought new value to the marketplace in this manner. Any new product under development should be evaluated with these aspects of value in mind. A generalized model of value, presented in Fig. 11.1 below, can be used to determine the areas of greatest need in the marketplace for a new agent and to provide guidance in product development. By talking with clinicians, patients, and others involved in current treatments and keeping this model in mind, the shortcomings of those current approaches can be evaluated and the sources of new incremental value can be determined.

Understanding the source of the value brought to the market by a new product is crucial to the development of the eventual marketing strategy. Using Fig. 11.1 as a guide, the potential sources of value can be determined for a product candidate and appropriate studies, both clinical and economic, can be designed to measure and demonstrate that value.

AN OVERVIEW OF ECONOMIC ANALYSIS FOR NEW TECHNOLOGIES

A thorough economic analysis should be used to guide the clinical research protocol to ensure that the end points measured are commercially relevant and useful. The analysis should describe important elements of the market to the firm, helping decision makers to understand the way decisions are made and providing guidance in affecting those decisions. Later, the results of economic analyses should inform and guide marketing and pricing decisions as the product is prepared for launch, as well as help customers to use the product efficiently and effectively.

To prepare a thorough economic analysis, researchers must first have a comprehensive understanding of the flow of patients, services, goods, and money through the various health care systems. This process should begin as soon as the likely indications for a new product have been identified and continue throughout the product's development. The first step is to create basic economic models of the current treatment for the disorder(s) for which the product is likely to be indicated. This step will be used to fine-tune financial assumptions and clinical development process, to assure that the clinical protocols are designed to extract the greatest clinical and commercial potential from a product. Separate models should be prepared for each indication and level if the product is likely to be used to treat more than one indication and/or several different levels of the same indication (e.g., mild, moderate, and severe).

The purpose of the basic model is to provide a greater understanding of the costs associated with the disorder, and to identify areas and types of cost that provide the greatest potential for the product to generate cost savings. For example, the cost of a disorder that currently requires a significant amount of laboratory testing offers the potential for savings, and thus better pricing, if the new product can reduce or eliminate the need for tests. Similarly, some indications are well treated, but the incidence of side effects is sufficiently high to warrant special attention. When developing a new agent, it is as important to understand the source of the value to be provided as it is to understand the clinical effects of the agent.

PHARMACOECONOMICS

The field of economic evaluation of medical technologies goes by several names, depending on the discipline of the researchers undertaking the study and the type of technology being measured. For pharmaceutical and biotechnology products, the field has settled on the name of pharmacoeconomics, and an entire discipline has emerged to fill the needs of the area. Contributions to the development of the field have come from several disciplines, including economics, pharmacy administration, and many of the behavioral sciences.

Pharmacoeconomics has been defined as "the description and analysis of the costs of drug therapy to the health care systems and society" (Townsend 1987). Clinical studies assess the efficacy of a biotechnology product; likewise, pharmacoeconomic studies help to evaluate the efficiency of biotechnologically derived drug. In a complete pharmacoeconomic assessment, both the costs and consequences are identified, measured, and compared with other available medical interventions. The increase in the health care expenditure in the United States has resulted in excessive demand for cost-containment measures. Managed care organizations are striving hard to control drug spending and other health care-related costs. Payers are moving from an open formulary system to a more closed formulary system, leading to additional emphasis on pharmacoeconomic assessment. Additionally, several states in the United States have passed laws in an attempt to increase transparency of developmental costs for new drugs and cap price increases post launch.

■ Importance of Pharmacoeconomics

To understand the importance of pharmacoeconomics in the biotechnology industry, it is necessary to understand the differences between the biotechnology products and traditional pharmaceutical products. Szcus and Schneeweiss (2003) have highlighted these differences. They observed that biotechnologically derived products are more expensive than traditional pharmaceutical products and that many biotechnology products are termed "orphan drugs" as they are used in small- or moderate-size patient populations. At times these products could be the only option to treat underlying disease condition. Given the high production costs and selling prices of biotechnology products, it is critical for these products to demonstrate adequate cost-effectiveness to justify their high cost. Therefore, pharmacoeconomics analysis is one of the major tools for payers to differentiate between a high-priced traditional pharmaceutical products and costly biotechnology products in certain instances.

Pharmacoeconomic analysis plays a crucial role in disease management. Chang and Nash (1998) outlined the role of pharmacoeconomics in disease management, which includes evaluation and identification of cost-effective medications for the treatment of particular disease conditions. This information can be and is used by payers and hospital personnel to make potential formulary decisions. In such instances, drugs with unfavorable pharmacoeconomics evaluations are unlikely to remain on formularies or will be moved to a restricted status. In addition to formulary decisions, disease management programs often include clinical guidelines that are designed primarily on cost-effectiveness of medications Joshnson and Nash (1996). When communicated properly, economic analysis can lead physicians to change their prescribing behavior thus decreasing unexplained variation in the treatment of the same disease. Walkom et al. (2006) studied the role of pharmacoeconomics in formulary decision making and found growing importance of pharmacoeconomic evaluations in formulary decision making.

When used appropriately, pharmacoeconomics analysis should help us to answer questions such as:

- What drugs should be included in the outpatient formulary?
- Should these same drugs be included on a hospital formulary?
- What is the best drug for a particular disease in terms of efficacy and cost?
- What is the best drug for a pharmaceutical manufacturer to invest time and money?
- What are the relative cost and benefits of comparable treatment options?

To address the above questions, it becomes necessary for us to understand different costs considered in pharmacoeconomics analysis and the underlying techniques used to perform these pharmacoeconomic evaluations.

■ Understanding Costs

A comprehensive evaluation of relevant cost and consequences differentiates pharmacoeconomics from traditional cost-containment strategies and drug use evaluations. Costs are defined as the value of the resource consumed by a program or treatment alternative. Health economists use different costs in pharmacoeconomic evaluations, which can be grouped under direct costs, indirect costs, intangible costs, and opportunity costs.

In pharmacoeconomic evaluations, a comparison of two or more treatments extends beyond a simplistic comparison of drug acquisition cost. Including different costs, when appropriate, provides a more accurate estimate of the total economic impact of treatment alternatives and disease management programs in distinguished patients or populations.

Direct Costs

Direct costs are the resources consumed in the prevention or treatment of a disease. The direct costs are further divided into direct medical costs and direct nonmedical costs.

The direct medical costs include expenditures on drugs, medical equipment, laboratory testing, hospital supplies, physician visits, and hospitalization costs. Direct medical costs could be further divided into fixed costs and variable costs. Fixed costs generally represent the overhead costs and are relatively constant. Fixed costs include expenditures on rent, utilities,

insurance, accounting, and other administrative activities. These costs are often not included in the pharmacoeconomic evaluations because their use or total cost is unlikely to change as a direct result of a specific intervention. On the other hand, variable costs are an integral part of pharmacoeconomic analysis. Variable costs include drugs, fees for professional services, and supplies. These variable costs increase or decrease depending on the volume.

Direct nonmedical costs are out-of-pocket costs paid by patients (or their caregivers) for nonmedical services which are generally outside health care sector. Direct nonmedical costs included expenditure on transportation to and from the hospital, clinic or physician office, additional trips to emergency rooms, expenses on special diet, family care expenses, and other various forms of out-of-pocket expenses.

Indirect Costs

Indirect costs are those costs that result from morbidity or mortality. Indirect costs assess the overall economic impact of an illness on a patient's life. Typical indirect costs include the loss of earnings due to temporary or permanent disability, loss of income to family member who gave up their job temporarily or permanently to take care of patient, and loss in productivity due to illness. Indirect medical costs are more related to patients and often unknown to or unappreciated by providers and payers.

Intangible Costs

Intangible costs are the most difficult to quantify in monetary terms. These costs represent the nonfinancial outcome of disease and medical care. The examples of intangible costs include pain, suffering, and emotional disturbance due to underlying conditions. Though these costs are identified in an economic analysis, they are not formally calculated. At times intangible costs are converted into a common unit of outcome measurement such as a quality-adjusted life-year (QALY).

Opportunity Costs

Opportunity costs are often discussed in the economic literature. Opportunity cost is defined as the value of the alternative that was forgone. In simple terms, suppose a person spends $100 to buy a drug to treat a particular disease condition, then the opportunity to use the same $100 to obtain a different medical intervention or treatment for the same disease condition, or for some nonmedical purpose, is lost. This is referred to as an opportunity cost. Although not often included in traditional pharmacoeconomic analysis, opportunity costs are often considered implicitly by patients when cost sharing (e.g., co-pays and coinsurance) is increased in a health benefit plan.

Method	Cost unit	Outcome unit
Cost of illness	Currency	Not assessed
Cost-minimization	Currency	Assumed to be equivalent in comparative groups
Cost-benefit	Currency	Currency
Cost-effectiveness	Currency	Natural units (life-years gained, mg/dL, blood glucose, mm Hg blood pressure)
Cost-utility	Currency	Quality-adjusted life-years or other utility

Table 11.1 ■ Economic evaluation methodologies

UNDERSTANDING PHARMACOECONOMIC METHODS

The purpose of this section is to provide an overview of pharmacoeconomic techniques currently used to evaluate drugs or treatment options. Table 11.1 represents the list of pharmacoeconomic methods. Selection of a particular technique depends on the objective of the study and outcome units which are compared. Grauer et al. (2003) stated that "the fundamental task of economic evaluation is to identify, measure, value and compare the costs and consequences of the alternatives being considered."

■ Cost of Illness (COI)

Cost of illness analysis is an important pharmacoeconomic tool to examine the economic burden of a particular disease. This technique takes into consideration the direct and indirect costs of a particular disease. A COI analysis thus identifies the overall cost of a particular disease in a defined population. Bootman et al. (1991) argue that COI analysis helps to evaluate the humanistic impact of disease and quantify the resources used in the treatment of disease prior to the discovery of new intervention. This information could be effectively used by pharmacoeconomic researchers to establish a baseline for comparison of new treatment or intervention. COI analysis is not used to compare two alternative treatment options, but to estimate the financial burden of the disease under consideration. Thus, the monetary benefits of prevention and treatment strategies could be measured against the baseline value estimated by cost of illness. In essence, a COI analysis provides the foundation for the measurement of the economic consequences of any treatment for the disorder in question. For example, Segel (2006) points out that a study on the cost-effectiveness of donepezil, published in 1999, relied on a COI study of Alzheimer's disease published a few years earlier. Without the initial COI study the cost-effectiveness work would have been exponentially more difficult and costly.

■ Cost-Minimization Analysis (CMA)

Cost-minimization analysis is the simplest pharmacoeconomic evaluation technique. The primary objective of the cost-minimization analysis is to determine the least costly alternative. CMA is used to compare two or more treatment alternatives that are equal in efficacy. An example of CMA would be a comparison of branded product to a generic equivalent. It is assumed that the outcomes associated with the two drugs are equivalent; therefore, costs alone could be compared directly. The cost included in this economic evaluation must extend beyond drugs acquisition cost and should include all relevant costs incurred for preparing and administering drugs.

Argenta et al. (2011) performed a CMA to evaluate the direct costs of venous thromboembolism treatment with unfractionated heparin (UFH) and enoxaparin from the institutional perspective. The drug acquisition costs, laboratory tests, hospitalization costs, and drug administration costs were included to estimate the medical cost. Statistically nonsignificant differences were observed between unfractionated heparin and enoxaparin groups in the number of bleeding events, blood transfusion, and death. The daily cost per patient for UFH was $12.63 U.S. and for enoxaparin was $9.87 U.S. Depending on the mean time of use, the total cost for UFH was $88.39 U.S. as compared to $69.11 U.S. for enoxaparin. Therefore, it was concluded that enoxaparin provided higher cost saving as compared to unfractionated heparin for the treatment of hospitalized patients with venous thromboembolism.

■ Cost-Benefit Analysis (CBA)

In cost-benefit analysis, costs and benefits are both measured in currency. In a CBA all the benefits obtained from the program or intervention are converted into some currency value (e.g., US dollars or euros). Likewise all program costs are identified and assigned a specific currency value. At times the costs are discounted to their present value. To determine the cost-benefit of a program, the costs are subtracted from the benefit. If the net benefit value is positive, then it can be concluded that the program is worth undertaking from an economic perspective.

The results of the CBA could be expressed either as cost-benefit ratio or a net benefit. For example, a cost associated with a medical program is $1000, and the outcome/benefit resulting from the program is $9000. Therefore, subtracting the cost $1000 from the benefits $9000 will yield net benefit of $8000. When comparing many treatment alternatives, an alternative with the greatest net benefit could be considered as most efficient in terms of use of resources. In CBA, all costs and benefits resulting from the program should be included.

A typical use of CBA is in the decision of whether a national health benefit should include the administration of a specific vaccine. In this case the cost of vaccinating the population and treating a smaller number of cases of the disease would be compared with the costs that would be incurred if the disease were not to be prevented. At times, however, it is much more difficult to assign a monetary value to benefits. For example, the benefit of a patient's satisfaction with the treatment or improvement in patient's quality of life is very difficult to convert to a monetary sum. This presents a considerable problem. At times these variables are considered as "intangible benefits," and the decision is left to the researcher to include in final analysis. Because of this CBA is seldom used as a pharmacoeconomic method to evaluate a specific treatment, although many who perform different types of analyses often mistakenly refer to their work as "cost-benefit."

■ Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analysis is a method used to compare treatment alternatives or programs where cost is measured in currency and outcomes/consequences are measured in units of effectiveness or natural units. Therefore, cost-effectiveness analysis helps to establish and promote the most efficient drug therapy for the treatment of particular disease condition. The results of cost-effectiveness analysis are expressed as average cost-effectiveness ratios or as the incremental cost of one alternative over another. CEA is useful in comparing different therapies that have the same outcome units, such as an increase in life expectancy or decrease in blood pressure for hypertension drugs. CEA is a frequently used tool for evaluating different drug therapies to treat a particular disease condition. This type of analysis helps in determining the optimal alternative, which is not always the least costly alternative. CEA has an advantage that it does not require the conversion of health outcomes to monetary units.

CEA is often used to guide formulary management decisions. For example, consider a biotechnology product "X" that provides a 90% efficacy or cure rate for a specific disorder. The total treatment cost for 100 patients with product X is $750,000. Likewise assume that another biotechnology product "Y" prescribed for the same disorder shows 95% efficacy; however, the treatment cost of 100 patients with product Y is $1,000,000. The average cost-effectiveness ratio (ACER) of product X is calculated by dividing the cost $750,000 by the outcome, 90 cures, to yield an ACER of $8333 per cure. Similarly the ACER for product Y is $10,526 per cure. From this analysis, it is evident that using product Y would cost an additional $2192 per cure,

which is the difference between ACERs of product Y and product X.

At times the incremental cost-effectiveness ratio (ICER) is important in drug selection decisions. From the above example, to calculate the ICER, total cost of product X ($750,000) is subtracted from total cost of product Y ($1,000,000). This is then divided by the cures from product X (90), subtracted from the cures resulting for product Y (95). Therefore, the incremental cost for each additional cure with product Y is $250,000 divided by 5 cures or $50,000 per cure. The incremental cost-effectiveness ratio poses the question of whether one additional cure is worth spending $50,000. The additional cost of cure might be justified by the severity of the disease or condition; this is a decision that is best made with the full knowledge of the economic implications. This provides an example of a situation in which the economic analysis is used to help guide the decision, but not to make the decision. Table 11.2 represents the ICER for product X and Y.

Good examples of CEAs are the recent comparisons of the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors Praluent® (alirocumab) and Repatha® (evolocumab) or ezetimibe with statin therapy. PCSK9 inhibitors were approved in 2015 to lower low-density lipoprotein levels in individuals with heterozygous familial hypercholesterolemia (FH) or artheroscclerotic cardiovascular disease (ASCVD). Annual acquisition costs of alirocumab and evolocumab were $14,600 U.S. and $14,100 U.S. respectively at launch, which were significantly higher than statins and ezetimibe, for which generic equivalents are available. Kazi et al. (2016) calculated the lifetime major adverse cardiovascular events (MACE), incremental cost per quality-adjusted life-year (QALY), and total cost to the US health care spending over 5 years. They estimated that adding PCSK9 inhibitors to statin therapy compared to ezetimibe prevented 316,300 MACE at a cost of $503,000 U.S. per QALY in heterozygous FH, and prevented 4.3 million MACE at a cost of $414,000 U.S. per QALY in ASCVD. Use of PCSK9 inhibitors would reduce costs for cardiovascular care by $29 billion U.S. over 5 years, but add drug costs worth $592 billion U.S. Since PCSK9 inhibitors cost four to five times higher than the generally accepted $100,000 U.S. per QALY threshold, the researchers concluded that annual acquisition costs of PCSK9 inhibitors would have to be reduced to $4536 U.S. in order for them to be cost-effective. Re-analysis of the model with recent data on ASCVD also shows that PCSK9 inhibitors are not cost-effective at 2017 prices (Kazi et al. 2017). Arrieta et al. (2017a, b) have made similar conclusions regarding the cost effectiveness of PCSK9 inhibitors compared to standard statin therapy.

Product	Efficacy (%)	No. of patients treated	Total costs ($)	ACER ($)	ICER ($)
Product X	90	100	750,000	8333	50,000
Product Y	95	100	1,000,000	10,526	

Table 11.2 ■ Incremental cost effectiveness ratio (ICER) for two products

■ Cost-Utility Analysis (CUA)

Cost-utility analysis was developed to factor quality of life into economic analysis by comparing the cost of the therapy/intervention with the outcomes measured in quality-adjusted life-years (QALY). The QALYs are calculated by multiplying the length of time in a specific health state by the utility of that health state—the utility of a specific health state is, in essence, the desirability of life in a specific health state compared with life in perfect health. A utility rating of 0.9 would mean that the health state in question is 90% as desirable as perfect health, while a utility rating of 0.5 would mean that health state is only half a desirable. Death is given a utility score of 0.0. The results of a CUA are expressed in terms of cost per QALY gained as a result of given treatment/intervention. CUA is beneficial when comparing therapies that produce improvements in different or multiple health outcomes. Cost per QALY can be measured and evaluated across several different treatment scenarios, allowing for comparisons of disparate therapies.

Goulart and Ramsey (2011) evaluated cost utility of Avastin® (bevacizumab) and chemotherapy versus chemotherapy alone for the treatment of advanced non-small-cell lung cancer (NSCLC). Avastin is currently approved for the treatment of NSCLC in combination with chemotherapy based on 2 months median survival proved in clinical trials. Researchers developed a model to determine quality-adjusted life-years and direct medical cost incurred due to treatment with bevacizumab in combination with chemotherapy. The utilities used in calculating QALY were obtained from the literature and costs were obtained from Medicare. The results of the study showed that bevacizumab is not cost-effective when added to chemotherapy. It was found that bevacizumab with chemotherapy increased the mean QALYs by only 0.13 (roughly the equivalent of 1.5 months of perfect health), at an incremental lifetime cost of $72,000 U.S. per patient. The incremental cost-utility ratio (ICUR) was found to be $560,000 U.S./QALY. The results of these analyses could be potentially used by payers while allocating resources for the treatment of NSCLC care. Table 11.3 represents the base case results of cost-utility analysis.

Outcomes	CPB	CP	Differences
Effectiveness			
Life expectancy (years)	1.24	1.01	0.23
Progression-free survival (years)	0.72	0.47	0.25
QALYs	0.66	0.53	0.13
Lifetime costs per patients (US$)[a]			
Drug utilization	70,284.75	646.96	69,637.79
Drug administration	4239.87	1495.24	2744.63
Fever and neutropenia	25.32	4.37	20.95
Severe bleeding	19.65	1.33	18.32
Other adverse events	39.06	32.09	6.97
Outpatient visits	1017.90	609.41	408.49
Progressive disease	40,283.71	41,500.96	−1217.25
Total	115,910.26	44,290.36	71,619.90
ICER (US$/life-years gained)			308,981.58
ICUR (US$/QALY gained)			559,609.48

CP carboplatin and paclitaxel, *CPB* carboplatin, paclitaxel, and bevacizumab, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *QALYs* quality-adjusted life-years
[a]Cost in 2010 US dollars

Table 11.3 ■ Base case results of cost-utility analysis

SOURCES OF ECONOMIC VALUE

The economic value of the product may have elements besides the basic economic efficiency implied by the break-even level just discussed. Quality differences, in terms of reduced side effects, greater efficacy, or other substantive factors, can result in increases in value beyond the break-even point calculated in a simple cost comparison. Should these factors be present, it is crucial to capture their value in the price of the product, but how much value should be captured?

It is important to recognize that a product can provide a significant economic benefit in one indication but none in another. Therefore, it is prudent to perform these studies on all indications considered for a new product. A case in point is that of epoetin alfa (EPO). EPO was initially developed and approved for use in dialysis patients, where its principle benefit is to reduce, or even eliminate, the need for transfusion. Studies have shown that EPO doses that drive hematocrit levels to between 33 and 36% result in significantly lower total patient care costs than lower doses of EPO or none at all (Collins et al. 2000). The same product, when used to reduce the need for transfusion in elective surgery, however, has been shown not to be cost-effective (Coyle et al. 1999). Although EPO was shown to reduce the need for transfusion in this study, the cost of the drug far outweighed the savings from reduced transfusions as well as reductions in the transmission and treatment of blood-borne pathogens. Economic efficiency is not automatically transferred from one indication to another.

The lack of economic savings in the surgical indication does not necessarily mean that the product should not be used, only that users must recognize that in this indication use results in substantially higher costs while in dialysis it actually reduces the total cost of care.

FUTURE US HEALTH CARE CHANGES

Payers within the US health care system have begun to use similar methods of evaluation. Although it cannot be stated with certainty that the US system will adopt this approach to coverage wholeheartedly, the consistent news reports of new drugs costing tens, and hundreds, of thousands of dollars would indicate that the importance of delivering demonstrable value will increase in that market as well. Several states in the US have taken steps to control or increase transparency in drug pricing. New York state passed a law in 2017 which enables authorities to determine value-based prices for high-cost drugs, and then negotiate for additional rebates to achieve this price for its Medicaid program (Hwang et al. 2017). Other states have passed bills that require manufacturers to justify price increases above a certain threshold or publish research and development costs for new drugs (Sarpatwari et al. 2016).

In the pharmaceutical marketing environment of the foreseeable future, it is wise to first consider determining the true medical need for the intervention. Then, if the need is real, to consider surrendering some value to the market—pricing of the product at some point below its full economic value. This is appealing for several reasons:

- The measurement of economics is imprecise and the margin for error can be large.
- If the market is looking for lower costs, filling that need enhances the market potential of the product.
- From a public relations and public policy perspective, launching a new product with the message that it provides savings to the system can also provide positive press and greater awareness.

■ Biosimilars

Many drugs used to diagnose and treat diseases are biological products that until recently were available

from a singular manufacturer. The first biosimilar (a product that is highly similar to the original biological product, described in more detail in Chap. 12 in this textbook) was Zarxio® (filgrastim-sndz), launched by Sandoz in 2015 as a biosimilar to Neupogen® (filgrastim). Subsequently, the biosimilars Inflectra® (infliximab-dyyb) and Renflexis™ (infliximab-abda) for Remicade® (infliximab) were launched in 2016 and 2017 respectively. Like generic alternatives launched at a discounted price to their branded counter-parts, Zarxio and Inflectra were launched at a 15% discount to Neupogen and Remicade respectively. Renflexis was priced at a 35% discount to Remicade and 20% discount to Inflectra.

Biomilars tend to take much longer than and may be more or equally expensive to develop as their original comparators. However, the current health care system and payers anticipate new biosimilars to be priced less than their original products; an expectation that developers and manufactures of biosimilars need to keep in mind as they pursue R&D of these products. Biosimilars have the potential to reduce overall health care costs spent on biological products compared to their original products; however, their pricing and value and ultimately commercial success remains to be examined. It remains to be seen if the recently approved, but yet to be launched biosimilars, Erelzi™ (etanercept-szzs), Amjevita™ (adalimumab-atta), Cyltezo™ (adalimumab-adbm), Mvasi™ (Bevacizumab-awwb), Ogivri™ (trastuzumab-dkst), and Ixifi™ (infliximab-qbtx) will also be priced at a discount to their reference products.

CONCLUSIONS

As societies continue to focus on the cost of health care interventions, we must all be concerned about the economic and clinical implications of the products we bring into the system. Delivering value, in the form of improved outcomes, economic savings, or both, is an important part of pharmaceutical science and marketing. Understanding the value that is delivered and the different ways in which it can be measured should be the responsibility of everyone involved with new product development. Further, all of this needs to be done with keeping the changing health care policy and regulatory landscape in mind.

■ Questions and Answers

1. When conducting pharmacoeconomic evaluations, typically the following costs are calculated or included in the analyses: direct, indirect, intangible and opportunity costs. Define these cost types and give examples to describe them.
   - Direct costs—They are the resources consumed in the prevention or treatment of a disease. Direct costs are further divided into:
     - Direct medical costs—These include expenditures on drugs, medical equipment, laboratory testing, hospital supplies, physician visits, and hospitalization costs. Direct medical costs are further divided into:
       - Variable costs—They are an integral part of pharmacoeconomic analysis. Variable costs increase or decrease depending on the volume, and include drugs, fees for professional services, and supplies.
       - Fixed costs—These include expenditures on rent, utilities, insurance, accounting, and other administrative activities. Fixed costs are not included in pharmacoeconomic evaluations because their use or total cost is unlikely to change as a direct result of a specific intervention.
     - Direct nonmedical costs—They are costs are out-of-pocket costs paid by patients (or their caregivers) for nonmedical services, and include expenditure on transportation to and from the hospital, clinic or physician office, additional trips to emergency rooms, expenses on special diet, family care expenses, and other various forms of out-of-pocket expenses.
   - Indirect costs—They are costs that result from morbidity or mortality. Indirect costs typically include the loss of earnings due to temporary or permanent disability, loss of income to family member who gave up their job temporarily or permanently to take care of patient, and loss in productivity due to illness.
   - Intangible costs—They represent the nonfinancial outcome of disease and medical care, and are the most difficult to quantify in monetary terms. Examples include pain, suffering, and emotional disturbance due to underlying conditions. Intangible costs are identified but not formally calculated in an economic analysis. At times they are converted into a common unit of outcome measurement such as a quality-adjusted life-year (QALY).
   - Opportunity costs—They are defined as the value of the alternative that was forgone due to the purchase of a medical treatment. Opportunity costs are *typically not included* in traditional pharmacoeconomic analysis.

2. List the five pharmacoeconomic techniques used to examine a new medical technology or treatment option?
   - Cost of Illness (COI)
   - Cost-Minimization Analysis (CMA)
   - Cost-Benefit Analysis (CBA)
   - Cost-Effectiveness Analysis (CEA)
   - Cost-Utility Analysis (CUA)
3. Cost-utility Analysis (CUA) includes outputs shown as QALY's. Define and describe QALY.
   - QALYs stand for Quality Adjusted Life Years. The QALYs are calculated by multiplying the length of time in a specific health state by the utility of that health state—the utility of a specific health state is, in essence, the desirability of life in a specific health state compared with life in perfect health. The results of a CUA are expressed in terms of cost per QALY gained as a result of given treatment/intervention.
4. Which method is used most often by insurance company payers to make product P&T formulary decisions? Why?
   - The cost-effectiveness analysis (CEA) is often used to guide formulary management decisions because:
     – The CEA does not require the conversion of health outcomes to monetary units.
     – The CEA helps in determining the optimal alternative, which may not always the least costly alternative.

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SUGGESTED READING

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