Anticipating the Future: How the Emergence of Innovative Biologic Agents Impacts Benefit Design, Utilization, and Provider Relations

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ABSTRACT

OBJECTIVE: To review the impact of biologic therapies on commercial and government payers.

SUMMARY: Biologic agents, a mainstay in the treatment of cancer and immunopathologic conditions, are being used for an expanding number of indications, and new agents are being developed for use in many other diseases. These biologic agents have the potential to improve patient quality of life and the overall quality of care with minimal risk of adverse events. Many of these agents require administration via nontraditional methods and are priced at a premium, compared with existing therapies. Consequently, both commercial and government payers must devise strategies that simultaneously ensure access to these agents while minimizing their overall cost impact. Several tools are available to payers to achieve these goals, including aggressive formulary management, drug-use evaluation, and the use of specialty pharmacy services.

CONCLUSION: With appropriate planning and oversight, the value of biologic therapy can be optimized in the managed care setting.

KEYWORDS: Biologic therapy, Health care quality, Managed care, Injectable drug, Infused drug, Reimbursement

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Emergence of Innovative Biologic Agents

Innovative biologic agents that target specific molecular events involved in disease processes have entered clinical practice with the promise of offering safe, effective, and prolonged therapeutic benefits to millions of patients. Because of the relatively recent emergence of these agents, a standardized nomenclature has yet to be established. Consequently, several terms are used interchangeably to identify these new drugs, including biologic agents, biopharmaceuticals, biotechnology products, specialty pharmacy products, and bioengineered products.1 Adding to the confusion is the wide variety of entities produced via biotechnological means and used in the diagnosis, prevention, and treatment of disease, including vaccines, gene therapies, and monoclonal antibodies. Moreover, biologic agents are classified on the basis of their molecular structure, mode of administration (e.g., injected or infused), physical size, therapeutic or diagnostic use, mechanism of action, and manufacturing process. As a result, a confusing array of terms is used to describe this important emerging field.

Growth in the Biologic Agents Market

More than 325 million people worldwide have been treated with at least one of the more than 155 biotechnology drugs and vaccines approved by the U.S. Food and Drug Administration (FDA).2 Today, there are more than 370 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases.2 Nearly half of the biotechnology medicines under development are being evaluated for use in cancer.3 Other common disease targets include infectious diseases, autoimmune disorders, Alzheimer’s disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis. Of the biotech medicines on the market, 70% were approved in the

FIGURE 1  New Biotechnology Drug Approvals and Indications by Year: 1982-2002

last 6 years. There are nearly 1,500 biotechnology companies in the United States, and it is one of the most research-intensive industries in the world. Consequently, the number of biopharmaceuticals approved for clinical use is expected to increase significantly in the coming years. Figure 1 depicts the number of new biologic drug approvals from the years 1982 to 2002.

### Economic Impact of Biologic Agents

Biologic agents have a significant economic impact on health care. Sales of biotechnology products generated worldwide revenues of $34.8 billion in 2002. Historically, revenue growth has been led by sales of insulins and hematopoietic growth factors. However, the market is projected to nearly double in size to $50 billion, driven by growth from new monoclonal antibodies, which are expected to replace the erythropoietins as the largest class of biologic agents.

### Biologic Agents: Challenging the Status Quo

Biologic agents are challenging traditional methods of cost containment used by the health care industry. Some of the new issues that biologic agents have introduced include consideration for the nature of the diseases being treated, route of administration, acquisition and monitoring costs, and distribution channels for these products. An additional challenge to managing biologic agents from a health care perspective is the lack of standardized data collection and analysis systems due to the relative novelty and historically low volume of their use. Unlike traditional drug therapies that target a broad patient base, biologic therapies have historically targeted narrow markets that include patients with more severe disease or with rare or uncommon diseases. Currently, the majority of available biologic therapies have been developed for use in patients who have cancer and immune-mediated diseases (Figure 2). However, it is expected that nearly all diseases will be targeted in the near future.

### Biologic Agents and Managed Care

The increasing number and use of biologic agents is already having an effect on both commercial and government managed care organizations (MCOs). How these payer groups respond to the dramatic increase in use and costs of these agents will have a profound effect on their ability to continue to provide affordable drug coverage to their members. Another consideration that must be addressed by MCOs includes the shift of biologic drug administration from inpatient to outpatient venues and the subsequent reallocation of costs from the medical to the pharmacy budget.

### Economic Implications for Managed Care

The current per-member-per-month (PMPM) drug costs for commercial MCO enrollees ranges from $20 to $30. It is estimated that approximately 30 million patients are candidates for biologic therapy in the United States. Therefore, it is expected that demand and use of biologic drugs will add between $2.50 and $7.50 PMPM in costs in 2004, depending on the drugs used in the economic models. Even with variability in utilization measures across the managed health care industry, such as the number of patients treated with these agents and the amount of money spent on these agents, most payers definitively agree that both measures of growth will increase exponentially in the next decade.

### Impact on Commercial Payers

Biotechnology drug costs are beginning to constitute an increasingly larger portion of the MCO pharmaceutical budget. Nearly 90% of current biologic agents and those in late-stage development require administration by injection or infusion, and 70% of these agents must be administered by a health care professional either on an inpatient or outpatient basis. It is estimated that injectable medications cost 10 times more than oral prescription drugs. In order to document the advantages of biologic agents relative to traditional drug therapy and justify the higher costs, it will be important to identify and track the use of biologic agents through the development and implementation of integration data collection and management systems. In addition, these drugs have primarily been associated with oncology and transplantation and have been administered in hospitals and infusion clinics. Newer biologic drugs are frequently administered by the patient at home. At-home administration is shifting the place of dispensing from hospitals and infusion clinics to home infusion companies, specialty pharmacies, and retail pharmacies, redirecting costs from the medical to the pharmacy budget.

### Management Challenges

To effectively manage the use of biologic agents, commercial payers must accurately analyze drug use across their organization. An accurate and timely drug-use analysis is challenged by poorly inte-
Strategies for Managing the Use of Biologic Agents

Benefit Design Changes

In an effort to ensure continued coverage of biotechnology drugs and maintain affordable premiums, MCOs have developed several strategies to manage utilization and minimize costs. Redesigning the pharmacy benefit is one such strategy. Pharmacy benefits often do not include coverage of drugs for cosmetic uses, smoking cessation, infertility, weight loss, or life-style uses. These condition exclusions have recently been expanded to include the use of growth hormone for children diagnosed with idiopathic short stature and self-injectable drugs, with the exception of insulin for Centers for Medicare and Medicaid Services (CMS) members. Some plans have also implemented separate biologic drug or self-injectable drug rider policies. Finally, it is possible that, if payers become unable to maintain financial viability due to drug costs, the drug benefit may evolve to include only catastrophic coverage.

Cost sharing is another strategy used to manage utilization of biologic agents. Many MCOs include in-office injectable drug costs in global capitation-physician contracts, but accurate predictions of year-to-year costs is difficult, and shared risk agreements between MCOs or employers and pharmacy benefit management companies are becoming less common. Recently, MCOs have begun to shift costs to their enrolled members through the use of special injectable copays and coinsurance programs. Programs that assign a fixed dollar amount equal to 2 times the highest oral drug copay, creation of a special tier for biologics, or adding a coinsurance of 20% or higher are all examples of cost shifting that may help to manage utilization and control costs. However, since the costs of many of these drugs average $1,000 to $1,500 per month, many members will not be able to maintain a 20% to 40% coinsurance payment, with possible ramifications of member or client dissatisfaction, an increase in lawsuits demanding more complete coverage, or a larger number of patients enrolling for state assistance.

Another avenue to control biologic drug use may be through partnership with pharmacy services that specialize in injectable drug distribution. Specialty pharmacies are designed to assure payment, ensure that a patient meets the criteria for use, and assure delivery to the patient or physician office. These pharmacies may also enhance the quality of care by offering disease management initiatives, patient education, and patient-adherence programs.

Factors That May Influence Choice of Therapy

Retrospective drug-use evaluation (DUE) with physician educational pieces, implementing prior-authorization (PA) guidelines, and placing biotechnology drugs on a preferred drug list are other tools that help MCOs manage biologic drug use. All of these methods provide the plan with the ability to influence the choice of drug used. However, health plans are not able to control all aspects of biologic drug prescribing. For example, a physician with a capitated agreement that includes in-office drugs may choose to prescribe a drug that can be self-administered subcutaneously versus one that requires an intravenous administration. Alternatively, a fee-for-service provider may have a financial incentive to prescribe a drug that produces a profit based on both the acquisition fee and the professional fee for drug administration. Regulatory and legislative mandates may also affect the choice of therapy. For example, CMS covers only agents they consider to be non-self-administered therapies for the treatment of multiple sclerosis. The 2 agents that meet this criteria are interferon beta-1a (administered via intramuscular injection and therefore deemed non-self-administered by CMS) and mitoxantrone (administered via infusion). Consequently, some MCOs choose to use only the CMS covered product in order to shift costs to the government payer.

DUE is a structured, ongoing process that determines how and under what conditions a product is being used. A DUE can be either prospective or retrospective (Figure 3). Evidence-based PA is a component of the prospective DUE process. Authorization criteria include diagnosis criteria, which identify the indications for which the drug can be used (both FDA approved and off-label use); prescriber criteria, which may identify which health care professionals are approved to prescribe specific formulary drugs; and drug-specific criteria, which may identify previous agents tried for the condition, approved doses, frequency of administration, and duration of therapy. Criteria should be updated as additional high-quality data becomes available. For cases in which a drug poses
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drug lists can be created and PA used to manage or enforce appropri- 
what benefit can be adapted for use with biologic agents. Preferred 
apy to include in a treatment guideline.

many of the factors that may be considered when selecting a ther-
go ong therapy considerations and evaluations. Table 1 identifies 
choice of patient, and monitoring. Guidelines should also address 
ong therapy for a patient, when prescribing biologic agents, a 
patient's teachability and willingness to participate in therapy 
should be assessed. This includes the ability to make regular trips 
to infusion centers or physician offices for drug administration and 
y any required monitoring. The patient's ability and willingness to 
pay for therapy also needs to be taken into consideration, particu-
larly since most biologic therapies require lifelong commitment for 
continued efficacy of the agent.

FIGURE 3 Schematic Illustrating the Steps Commonly Used to Conduct a Drug-Use Evaluation

TABLE 1 Factors to Consider When Selecting Therapies for Inclusion in Treatment Guidelines

- Percentage of patients responding and degree of response
- Rapidity of response (only in life or limb threatening or where disability occurs rapidly)
- Duration of response
- Ability to interrupt and restart therapy (planned intermittent administration, adverse drug reactions, nonadherence due to financial or other reasons)
- Need for cotherapies
- Frequency and severity of adverse reactions, including the possibility of infrequent unknown reaction with drugs studied or used in small populations
- Route, frequency, and time of administration
- Need for monitoring
- Costs (acquisition, monitoring, adverse reactions, administration, cotherapies, distribution, failure/alternative therapies)

potential efficacy, toxicity, or utilization issues or when it may be 
used off-label, the pharmacy and therapeutics (P&T) committee 
may be consulted when establishing the criteria.

Treatment guidelines are frequently used to direct prescribers 
to the most cost-effective therapies. This is particularly true when 
multiple drug therapies are available and the disease may be 
everventionally costly to treat. Quality guidelines are based on placebo-controlled or comparative trials or meta-analyses and include 
direction on the diagnosis, disease staging, choice of therapy, choice of patient, and monitoring. Guidelines should also address 
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many of the factors that may be considered when selecting a ther-
apy to include in a treatment guideline.

Several tools commonly used to manage the traditional phar-
acy benefit can be adapted for use with biologic agents. Preferred 

TABLE 1 Factors to Consider When Selecting Therapies for Inclusion in Treatment Guidelines

Government payers such as CMS are also being challenged by the 
emergence of biologic agents. CMS is faced with similar challenges 
in biologic pharmacy benefit management as private insurers.

In addition, as a government-sponsored agency, CMS must make 
coverage decisions under intense local and national political pres-
sure. CMS, as a purchaser of health care, is interested in determin-
ing if new therapies have clinical and cost advantages over existing 
ventions. Providing cost-effective coverage is particularly criti-
cally due to the extremely large number of patients enrolled in Medicare and Medicaid and the rapid growth of the programs.

Coverage increased from 19.1 million in 1996 to a projected 
40.6 million in 2002, a 113% increase. On average, the number of 
Medicaid enrollees in 2002 was estimated to be approximately 
40.6 million. Nationwide, CMS expenditures on all health care 
were $1,424.5 billion in 2001, a sum equivalent to 14.1% of the 
gross domestic product. Additionally, 20.5 million CMS patients 
received prescription drugs in 2001. Clearly, the increasing avail-
ability and use of innovative biologic agents has the potential to 
significantly increase CMS expenditures.

CMS Coverage and Reimbursement Process

CMS has a formal, explicit process to make coverage decisions on 
all products, including biologic agents, which is conducted at both 
the state and national levels in an increasingly interactive, trans-
parent, and scientific process. Coverage decisions are prompted by 
either external requests or are internally generated. External 
requests result from a request to review a national no-coverage 
decision or are prompted by the existence of a substantial variation
between the local and national coverage guidelines. Internally generated decisions are usually the result of the publication of an influential new study, the emergence of a significant technological advance with potentially major clinical or economic implications, or concerns about inappropriate use of a currently approved therapy.

CMS relies on high-quality, published scientific evidence to support all coverage decisions. This approach de-emphasizes intuition and unsystematic clinical experience and promotes open, explicit, and consistent coverage decisions. Using this process allows CMS to make coverage decisions that concentrate limited health care resources on interventions that improve health and avoids payment for therapies that are ineffective or promote harm.

CMS relies on both internal assessments of the evidence as well as external third-party reviews of the available data. Internal CMS technology assessments committees review the methodology and results of individual studies to determine the relative magnitude of benefits and harms of the therapy under consideration and if the conclusions can be applied to the general Medicare population. External technology assessments are conducted by the independent Agency for Healthcare Quality.

The Medical Technology Council (MTC) is an internal CMS committee that is charged with coordinating coverage, coding, and payment of CMS-approved benefits. This policy committee holds monthly meetings to review emerging technologies, provide resolution of problems spanning multiple policy components, and address general policy coordination issues. The MTC is also charged with providing CMS with an early alert for any noncovered therapies being widely utilized in the private sector.

Steps Involved in Gaining CMS Reimbursement

A 5-step process is implemented once CMS has decided to consider a therapy for reimbursement, including regulatory approval, determination of the statutory eligibility to be deemed a benefit, determination of the extent of coverage (local versus national), assignment of a reimbursement (billing) code, and distribution of the payment. This process is depicted in Figure 4.

All therapies considered for coverage by CMS must be approved by the FDA for at least one use. All covered interventions must, by law, fit into one of 55 statutory benefit categories that have been defined and approved by Congress under section 1862(a)(1)(A) of the Social Security Act. Once the FDA deems a product to be effective and approves its use, the pharmaceutical manufacturer agrees to pay CMS rebates in accordance with OBRA 90 (Omnibus Budget Reconciliation Act), then CMS covers the agent. For most pharmaceuticals, the state Medicaid programs administer the pharmacy benefit; they collect manufacturers’ rebates in all states except Arizona. The rebates are then split with the federal government, since CMS covers 53% of Medicaid expenditures on drugs.

**CMS Coverage of Biologic Agents**

Faced with the rapid growth of biologic therapies, CMS is faced with the challenge of providing enrollees access to these safe and effective therapies while at the same time managing costs and utilization to maintain fiscal viability. Unlike commercial plans that can severely restrict reimbursement based solely on cost considerations, or state Medicaid agencies that can make formulary decisions to enforce strict PA criteria before authorizing payment for an expensive drug, CMS does not include cost as a factor in determining what is reasonable and necessary when making coverage decisions. As described earlier, CMS coverage decisions are based primarily on an evidence-based review of the available data for currently marketed products. Like commercial plans, CMS does have the ability to shift the cost of biologic agents through the use of a coinsurance policy.

**Measuring Value and Quality in an Era of Pharmaceutical Innovation**

The current health care environment is influenced by an emphasis on performance with respect to cost and quality, an increased consumer voice in a market-driven health care system, and rapid introduction of innovative therapies. Because of these diverse and competing forces acting on the health care environment, the quantitative assessment of health care quality plays an increasingly important role in the determination of the overall value of a therapeutic intervention. The availability of reliable quality and value measurements is particularly critical to managed care decision makers as they evaluate the increasing numbers of new therapies and attempt to determine if these innovative products improve clinical outcomes with a cost-benefit ratio that is acceptable to providers, patients, and payers.
Organizations such as the National Committee for Quality Assurance (NCQA), a private, nonprofit organization established to improve health care quality, have taken the lead in coordinating efforts to improve health care quality by establishing a set of measurement principles and providing guidelines for the appropriate assessment of overall clinical effectiveness and quality in health care. The NCQA Health Plan Employer Data and Information Set (HEDIS) consist of a series of measures used to assess clinical effectiveness, including relevance, soundness, and feasibility of a clinical intervention. Relevance is defined as the overall importance of the intervention in promoting a patient’s health, the degree of variance in its implementation, and the ability to improve the practice. Soundness is defined as the relationship of the actual clinical practice to the accepted scientific evidence and feasibility that refers to costs, confidentiality, and the ability to collect and audit the data generated by implementation of the clinical intervention. Because these measures are specifically defined and implemented across a large portion of the managed care market, they permit close comparison of health plans over a wide range of clinical activities.

Identifying Cost Drivers and Measuring Value
Some of the factors contributing to the growth in health care spending are innovative therapies that are sold at premium prices to existing treatments. However, evidence does not support medical advances as a singular reason for the increased cost of health care. A recent study by Fisher et al. demonstrated that regional variations in health care spending were primarily accounted for by widespread use of discretionary medical services, particularly those provided by physician specialists. These investigators concluded that the use of discretionary medical services, such as more frequent physician visits in the inpatient setting, additional tests and minor procedures, and increased use of specialists and hospital resources, was sensitive to the local supply of specialty physicians and available hospital resources. In simple terms, regions where more specialists work and more hospital beds are available have the highest levels of spending on health care services. Interestingly, there was no evidence that greater use of these services is related to improved access to care, better-quality care, or better health outcomes or satisfaction. These results suggest that measuring performance via process and outcome measures alone is not enough to support health policy decisions, especially as new and effective medications enter the market place. The concept of value—that is, the balance between the cost and the benefit of particular interventions—must be included in any broad assessments of the appropriateness of health care services.

Assessing the Impact of Biologic Agents on the Quality of Health Care
Biologic agents hold the potential to improve the quality of health care. However, quality and value measures must be established in order to demonstrate cost-effectiveness of biologic agents in comparison with current therapy and must evolve as new therapies are introduced.

Summary
The number of biologic agents and the types of diseases in which they can be used is increasing rapidly. Most biologic agents have been proven to be safe and effective and often represent breakthrough therapy for conditions that have been historically difficult to treat. Biologic drugs have both a clinical and financial impact on managed care organizations. The strategies used by commercial and government payers to manage these agents will profoundly affect the ability of these organizations to provide drug coverage to their members at an affordable price. In addition, biologic agents have the potential to substantially alter the quality of health care, particularly in diseases historically resistant to traditional therapy. With appropriate planning and oversight, the value of biologic therapy can be optimized in the managed care setting.

REFERENCES