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

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An increasing number of biologic agents, most administered by injection in physician offices and other outpatient settings, are available to treat a variety of disease states, including asthma, cancer, HIV, multiple sclerosis, psoriasis, and rheumatoid arthritis. In addition, more than 350 experimental biologic drugs are in clinical trials. With the U.S. Food and Drug Administration (FDA) signaling that the speed at which these innovative therapies are reviewed for approval will increase, it is anticipated that a deluge of new biologic drugs will enter the market over the next 5 to 10 years. These innovative biologics offer the promise of effective treatment for patients who had exhausted all other options and have the potential to drastically reduce needs for expensive therapies such as hospitalization, surgery, and long-term supportive care.

Many health plans are focusing intently on the appropriate medical utilization of these drugs; however, these drugs pose a new set of challenges for insurers, health care systems, and pharmacy benefit managers. A number of factors complicate the integration of these new drugs into traditional health insurance plans, including the route of administration, injection or infusion, place of service, and the involvement of new providers such as specialty pharmacies. Complex finance and benefit issues, including cost allocation between pharmacy and medicine, copay structure, CMS mandates, and accurate claims processing, need to be addressed. Consequently, health care providers are faced with the dual challenge of providing increased access to these novel therapies while keeping premium increases to a minimum.

This program is designed to help pharmacists and managed care providers explore strategies that can be employed to manage the anticipated expense associated with the increased use of biologic agents. The management of expenses associated with the use of biologics requires a coordinated effort among several business units in the health care bureaucracy. Therefore, it is imperative that managed care providers, pharmacy decision makers, and others who are responsible for benefit design devise strategies that ensure appropriate utilization within the constraints of fiscal limitations.

Disclaimer
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this program is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this program should not be used by clinicians without evaluation of their patient's conditions and possible contraindications, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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Target Audience
This program has been designed to meet the educational needs of pharmacists and pharmacy administrators practicing in a managed care environment.

Learning Objectives
Upon completion of this program, participants will be better able to
1. discuss the impact of treatment with biologics on benefit design, provider relations, and quality of care in Medicare and managed care;
2. identify how Medicare coverage decisions affect managed care and other payers and their formularies;
3. explain the rationale for cost shifting, multi-tiered copays, prior authorization, and use of specialty pharmacy services to manage costs associated with biologic drugs; and describe the effectiveness and long-term value of biologic agents in different disease states; and
4. describe the effectiveness and long-term value of biologic agents in different disease states.
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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.3 Nearly half of the biotechnology medicines under development are being evaluated for use in cancer.4 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-
grated pharmacy and medical data management systems that can result in duplicate payment on one drug administration. This occurs due to difficulties in managing or creating databases that allow for integration of point-of-sale pharmacy claims with medical claims that may be processed at a later date. Particularly due to the high price of biologic agents, ensuring that claims are paid only once will be a critical component to effective long-term management. Since pharmacy claims are usually more comprehensive and mostly accurate as compared with medical claims, it may be prudent to create data management systems that permit a single payment per patient per drug administration. This feature can be built into the online pharmacy adjudication system and allows the physician or clinic to bill for these services, much like retail pharmacies currently operate.

### 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. Although there are many advantages to using these outsource partners, it is too soon to determine if they will provide cost savings since certain pharmaceutical manufactures have contracted with a limited number of specialty pharmacies, partially to closely manage distribution and ensure payment for these expensive drugs.

Many of these utilization and cost-management strategies may turn out to provide only short-term solutions. Long-term solutions, grounded in data from high-quality pharmacoeconomic studies, will allow MCOs to identify and implement valid economical approaches to therapy and help eliminate cost silos. This will allow for continued coverage of biologic drugs as part of appropriate treatment strategies based on value rather than price. Well-designed studies demonstrating the benefit of biologic agents with regard to patient quality of life and overall productivity are also critical to convincing payers to continue coverage of the biologic agent.

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

Diagnosis Criteria

- Treatment Guidelines
- Prescriber Criteria
- Drug-Specific Criteria

Define Drug-Use Criteria or Treatment Guidelines

Refine Drug-Use Criteria or Treatment Guidelines

Measure Outcomes of Patients With Disease

Compare Outcomes for Patients Treated vs. Those Not Treated According to Criteria/Guidelines

Disseminate Information to Clinical Staff

Educational Programs Evaluate Compliance Formulary Changes

### 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)

### Impact of Biologics on Government Payers

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 pressure. CMS, as a purchaser of health care, is interested in determining if new therapies have clinical and cost advantages over existing interventions. Providing cost-effective coverage is particularly critical, partially 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 availability 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, transparent, 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 avoid payments 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 benefit and harm 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, and 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.

* Requesters: beneficiaries, advocacy groups, carrier medical directors, professional societies, manufacturers.

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 hospitals, 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**

Case Study 1. Impact of Route of Administration, Distribution Channels, and Need for Cotherapy on Overall Cost: Rheumatoid Arthritis

A case study in rheumatoid arthritis (RA) was selected to demonstrate how differences in drug distribution channels, route of administration, and need for cotherapy affect the overall cost of the drug. RA is a chronic, disabling, autoimmune disorder affecting the peripheral joints. The disease is characterized by symmetric synovitis, erosion of cartilage and bony surfaces, and, ultimately, joint deformity and destruction. While episodes of inflammation wax and wane, decreasing in most patients over many years, radiographic evidence demonstrates that joint destruction continues to progress in an intermittent manner and disability continues to progress throughout the course of the disease. RA affects 1% of the U.S. population. It affects women 3 times as much as men, with the peak incidence of the disease occurring between the ages of 30 and 40 years. The incidence of disability reaches 25% within 6.4 years of diagnosis and 50% within 21 years. Total costs of RA in the United States were estimated to be $14 billion in 1998, with direct medical costs 2 to 3 times higher for RA patients than...
for age- and gender-matched controls. A diagnosis of RA is also associated with a substantial loss of income and a reduced work capacity. Yelin estimated that 50% of RA patients cannot function in their jobs within 10 years of the onset of the disease.

When Health Net of Arizona created its original RA prior-authorization (PA) criteria, only etanercept and infliximab were available for use. Currently there are 3 biotechnology agents approved for the treatment of RA (Table 1). At the time the RA prior-authorization criteria were developed, much of the data currently available that describes the durability of response for etanercept and infliximab and their effects on radiographic progression were not yet published. Additionally, because direct comparative trials that identified differences in clinical outcomes were also not available at the time, a decision was made to consider the drugs therapeutically equivalent. Coverage decisions for the 2 products centered on 3 main issues: dosing, administration, and the need for cotherapy. The PA criteria required a prescriber to provide evidence that one drug was superior to the other if coverage of the nonpreferred agent was requested.

Etanercept offered fixed dosing of 25 mg twice weekly versus the variable dosing of 3 mg/kg to 10 mg/kg every 8 weeks associated with infliximab therapy. Etanercept was self-administered via subcutaneous injection while infliximab required administration via intravenous infusion. Etanercept was distributed through the retail pharmacy network, allowing for quantity restrictions to be placed on the drug at the claims processor level. This distribution method also allowed for the collection of a drug copayment. Infliximab, on the other hand, was reimbursed through the medical claims system, making limitations on covered doses and frequency of dosing difficult. This situation was addressed by granting the pharmacy department access to the medical claims authorization and payment system, allowing limitations to be placed both on dose and frequency.

To arrive at a dollar amount that represented the total cost to provide each therapy, the acquisition cost of etanercept was compared with the acquisition cost of infliximab plus the administration costs and the physician professional fees incurred by the need for intravenous delivery. Acquisition costs for etanercept were controlled through the retail pharmacy network. While infliximab could be supplied to requesting physicians by the Health Net of Arizona contracted specialty injectable pharmacy at a slight discount, several fee-for-service physician specialists refused to participate in the specialty pharmacy program. These physicians purchased the drug through other vendors and were reimbursed by the health plan at significantly higher rates than those paid to our specialty pharmacy, increasing the overall cost of infliximab therapy. Physicians administering infliximab also charged professional fees for drug infusion and office visits. Several hospital-based infusion centers had contracts allowing charges 2 to 3 times in excess of the average wholesale price and an infusion fee. The required coadministration of methotrexate was added to the estimated costs of infliximab therapy as were anticipated costs for the potential need to treat infusion-related side effects.

Based on a review of dosing, frequency, route of administration, and need for cotherapy, PA criteria were developed that required that patients fail nonbiotechnology (e.g., traditional) disease-modifying antirheumatic drug therapy before the initiation of biologic therapy. Etanercept was identified as the preferred biotechnology agent because of its fixed 25 mg dose, fixed twice-weekly dosing interval, subcutaneous route of administration, lack of mandated methotrexate cotherapy, availability through retail community pharmacies, and billing through the pharmacy claims system. Strict dose and frequency limits were placed on both etanercept and infliximab. The limits on etanercept were enforced through authorization of monthly quantity limits. Limits on infliximab were initially difficult to enforce primarily because the drug was billed and reimbursed through medical claims. When possible, infliximab was supplied directly to physicians through a specialty injectable pharmacy provider that billed Health Net directly at a discounted rate. To avoid the excessive costs associated with hospital-based infusion clinics, urgent care centers were contracted to infuse infliximab for a fixed infusion rate.

The results of a retrospective, 12-month drug utilization review (DUR) in 647 patients over 12 years who received either etanercept or infliximab demonstrated that dosing may escalate with infliximab over time. Charts of patients under the care of 125 geographically distributed rheumatologists were reviewed. Results of the review indicated that 37% of patients were receiving infliximab maintenance doses above the starting dose of 3 mg every 8 weeks, while 100% of patients who were receiving etanercept maintained the starting dose of 25 mg twice a week (Table 2). The possibility of dose escalation with infliximab must be taken into account in comparative cost models.

### TABLE 2

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of Patients</th>
<th>Percent</th>
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<tbody>
<tr>
<td><strong>Etanercept</strong></td>
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</tr>
<tr>
<td>25 mg biw</td>
<td>352</td>
<td>100</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
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<tr>
<td>3 mg/kg q 6 weeks</td>
<td>3</td>
<td>1</td>
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<td>3 mg/kg q 8 weeks</td>
<td>195</td>
<td>66</td>
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<td>4 mg/kg q 6 weeks</td>
<td>62</td>
<td>21</td>
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<tr>
<td>5 mg/kg q 6 weeks</td>
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<tr>
<td>5 mg/kg q 8 weeks</td>
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<tr>
<td>6 mg/kg q 8 weeks</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>8 mg/kg q 8 weeks</td>
<td>3</td>
<td>1</td>
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</tbody>
</table>

*biw = biweekly; q = every.*

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Costs Associated With Topicals

Prevalence estimated at 8% of the U.S. population. Currently, it affects a much larger number of patients than RA, with the current existing options, but at a substantially increased cost. Asthma drugs that provide only marginal incremental clinical benefits over to emphasize the need to establish tight controls on the use of

This case study reviews data on a new biologic therapy for asthma drilling in professional or infusion fees.

For example, etanercept demonstrated that per-patient drug costs were slightly less with etanercept than with infliximab in the treatment of RA, without factor-

Summary

Dosing, the route of administration, and the need for cotherapy all influence the cost of therapy with biologic agents for the treatment of RA. Health Net's decision to prefer etanercept allowed for greater control of dosing and distribution. A retrospective analysis of Health Net of Arizona pharmacy and medical claims demonstrated that per-patient drug costs were slightly less with etanercept than with infliximab in the treatment of RA, without factoring in professional or infusion fees.

Case Study 2. Agents Offering Only Marginal Incremental Benefit: Asthma

This case study reviews data on a new biologic therapy for asthma to emphasize the need to establish tight controls on the use of drugs that provide only marginal incremental clinical benefits over existing options, but at a substantially increased cost. Asthma affects a much larger number of patients than RA, with the current prevalence estimated at 8% of the U.S. population. Currently, it is estimated that more than 31 million Americans are diagnosed with asthma at some point in their lives. Approximately 32% to 40% of patients with asthma report that asthma interferes with daily work, school, or social activities; 4% require a physician office visit each year; 0.6% are seen in the emergency department; and 0.17% are hospitalized. Despite this, the majority of patients with asthma who are prescribed controller drug therapy do not use one regularly. Fewer than 50% of patients with asthma do not use the controller therapy recommended by the national guidelines—inhaled corticosteroids.

Omalizumab, a humanized monoclonal anti-immunoglobulin E (IgE) antibody, was approved in 2003 as maintenance therapy of moderate to severe perennial allergic asthma. The inclusion criteria for the pivotal trials were strict. Patients were required to have a documented allergy to perennial allergens, a history of regular inhaled or oral corticosteroid use for a minimum of 3 months, and elevated IgE levels as well as be assessed by their physician as having uncontrolled disease. The trials required forced steroid dose reduction. The primary end point was the number of asthma exacerbations, which was defined as a doubling of the inhaled corticosteroid dose or a burst of oral steroids. Secondary end points included changes in pulmonary function tests, total beta-agonist use, and asthma symptom scores. Physician office visits, emergency department use, and hospitalizations were not primary or secondary end points and were not reported in the clinical trials. Differences in these end points were subsequently published in a separate analysis. Benefits from omalizumab therapy were observed during both the forced steroid reduction phases and the maintenance phases of the studies. Asthma exacerbations were reduced by approximately one half of an exacerbation per patient over 24 to 28 weeks, peak flow increased by approximately 30 L/min (6%) versus 10 L/min (2%) for placebo, and forced expiratory volume in 1 second improved 4% with active drug versus 1% with placebo. Symptom scores improved by almost 1 point (on a scale of 0 to 4), and albuterol inhalations were reduced by 1 puff per day. In the separate analysis, unscheduled office visits were reduced by 14 per 100 patient years, emergency department visits were reduced by 2 per 100 patient years, and hospitalizations were reduced by 3 per 100 patient years.

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**TABLE 3** Limitations of Traditional Therapies Used to Treat Psoriasis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Limitations</th>
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<tr>
<td><strong>Systemic Therapies</strong></td>
<td></td>
</tr>
<tr>
<td>• Cyclosporine</td>
<td>Hypertension, renal toxicity</td>
</tr>
<tr>
<td>• Methotrexate</td>
<td>Monitoring for hepatotoxicity, GI upset, bone marrow suppression, pulmonary toxicity</td>
</tr>
<tr>
<td>• Retinoids</td>
<td>Hyperlipidemia, hepatic toxicity, teratogenic</td>
</tr>
<tr>
<td><strong>Phototherapies</strong></td>
<td></td>
</tr>
<tr>
<td>• UVB/PUVA</td>
<td>Skin cancer (melanoma, nonmelanoma), photoaging, inconvenience</td>
</tr>
<tr>
<td><strong>Topicals</strong></td>
<td>Inconvenience, irritation, limited efficacy in moderate to severe psoriasis</td>
</tr>
</tbody>
</table>

UVB = ultraviolet B radiation.
PUVA = combination of the photosensitizing drug psoralen (P) with ultraviolet A (UVA) radiation.


**TABLE 4** Costs Associated With Topicals and Phototherapy for Psoriasis

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Cost ($) per Month</th>
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</thead>
<tbody>
<tr>
<td>Phototherapy 3 times weekly</td>
<td>1,523</td>
</tr>
<tr>
<td>Cyclosporine (generic) 100 mg bid to tid</td>
<td>328.00-491</td>
</tr>
<tr>
<td>Methotrexate (generic) 15 mg q week injectable liquid taken orally or tablets</td>
<td>6.84-540</td>
</tr>
<tr>
<td>Soriatane (Acitretin) 25 mg to 50 mg qd</td>
<td>4.66-931.80</td>
</tr>
<tr>
<td>Calcipotriene (Dovonox) applied 120 gm bid</td>
<td>243.60</td>
</tr>
<tr>
<td>Clobetasol (generic) applied 60 gm qd</td>
<td>61.80</td>
</tr>
</tbody>
</table>

*2003 Medicare allowable. CPT 96913: Photochemotherapy (Goeckerman and/or PUVA) for severe photosensitive dermatoses requiring at least 4 to 8 hours of care under direct supervision of the physician (includes application of medication and dressings).

bid = twice a day; tid = 3 times a day; q = every; qd = every day.

Omalizumab is administered subcutaneously and can be self-administered. However, omalizumab therapy is usually initiated in the physician’s office and then either continued in office or transitioned to the home. The dose and frequency of administration of omalizumab is based on body weight and pretreatment serum IgE levels. The drug is administered either monthly or every other week. Using average wholesale pricing (AWP) pricing, the 1-year cost of omalizumab therapy for 100 patients (100 patient years) with similar weights and IgE levels as those seen in clinical trials would be between $1.4 million and $2.8 million. A review of published clinical trials found that omalizumab therapy prevented no more than 3 visits each to a physician’s office, emergency room, or hospital per 100 patient years.16 It was determined that omalizumab therapy provided only a marginal incremental benefit at a significant cost. Therefore, strict PA criteria were created that require a patient to have an adequate response to dual controller therapy, including an inhaled corticosteroid and evidence of increased resource utilization such as emergency department visits or hospitalization, prior to approval of coverage for omalizumab.

Summary
It is expected that an increasing number of biologic agents will become available to treat conditions such as asthma, traditionally managed at the primary care level. While future products may offer substantial clinical benefits over available therapies, it is important to establish tight controls on the use of drugs that provide only marginal incremental, clinical benefits over existing options, but at a substantial increase in cost.

Case Study 3. Clinical Efficacy and Cost of Therapy: Psoriasis

This case study demonstrates the relationship between clinical efficacy and the cost of therapy with biologic agents in the treatment of moderate to severe psoriasis. Psoriasis is an inflammatory disease of the skin, with an estimated prevalence of nearly 3% of the U.S. population.17 According to the National Psoriasis Foundation (NPF), approximately 4.5 million Americans suffer from psoriasis, with up to 260,000 new cases diagnosed each year. The average age of onset is 28 years. Each year, psoriasis leads to nearly 300,000 visits to dermatologists and 350 deaths.17 In addition, nearly 400 patients annually are deemed permanently disabled because of psoriasis.17

Approximately 30% of patients are considered to have moderate to severe disease, defined as having 10% or greater of their body surface area involved or localized involvement of areas such as the face, genitals, palms, or soles, that significantly interferes with their work or daily activities.18 Up to 30% of patients may also have joint involvement or psoriatic arthritis, a condition more prevalent in patients with severe skin involvement.17 The clinical course of psoriasis is highly variable, with periods of remission and relapse occurring over a lifetime and patients often requiring decades of therapy.

The American Academy of Dermatology (AAD) recently published a consensus statement on psoriasis therapies that called for more aggressive treatment. Topical corticosteroids remain a mainstay of therapy in patients with mild disease over limited body surface area. Topical steroids can also be used in moderate to severe psoriasis as initial therapy when the disease is limited to small areas.

The AAD consensus statement recommends that systemic therapies be considered as first-line for patients with moderate to severe psoriasis. Systemic therapies include but are not limited to ultraviolet B light therapy, PUVA (a combination of the photosensitizing drug psoralen [P] with ultraviolet A [UVA] radiation), methotrexate, cyclosporine, and soriatane. The choice of systemic therapy should be based on the type of psoriasis, availability of treatment sites, patient characteristics such as child bearing age, potential adverse effects, and cost to the patient.

Addition of biologics to the “tool box” of first-line treatment options in candidates for systemic therapy has been recommended in the AAD consensus statement.19 The NPF has created a treatment algorithm to guide practitioners in the use of photo-
 Injectable Biologic Case Studies

### TABLE 5  Summary of PASI End Points From Placebo-Controlled Trials in Patients With Moderate to Severe Psoriasis

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>PASI 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alefacept 15 mg q week x 12 weeks*</td>
<td>0.21</td>
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<tr>
<td>Efalizumab 1 mg/kg q week x 12 weeks*</td>
<td>0.22</td>
</tr>
<tr>
<td>Etanercept 25 mg twice a week x 12 weeks*</td>
<td>0.34*</td>
</tr>
<tr>
<td>Etanercept 50 mg twice a week x 12 weeks*</td>
<td>0.49*</td>
</tr>
<tr>
<td>Etanercept 50 mg twice a week x 12 weeks followed by 25 mg twice a week x 12 weeks†</td>
<td>0.49*</td>
</tr>
</tbody>
</table>

PASI 75 = 75% improvement in the Psoriasis Area and Severity Index.  
* Etanercept is currently under FDA review for approval for use in moderate to severe psoriasis.  
† 50 mg biweekly for first 12 weeks titrated to 25 mg biweekly for 12 weeks.

Data derived from:  

Table adapted from:  

### FIGURE 2  Annual Cost per Unit of Clinical Benefit (as Measured by the PASI Score) for Alefacept, Efalizumab, and Etanercept in the Treatment of Moderate to Severe Psoriasis

![Graph showing annual cost per unit of clinical benefit for different treatments]

* Represents annual cost per unit of clinical benefit and not drug acquisition cost.


Evaluating comparable efficacy of the 3 current biologic therapies that have sufficient clinical data for the treatment of psoriasis (i.e., etanercept, efalizumab, and alefacept) is difficult because of the lack of head-to-head studies and the limited duration of the clinical trials. However, a review of the currently available data from placebo-controlled clinical trials indicates that etanercept produces higher PASI 75 (75% improvement in the Psoriasis Area and Severity Index) response rates than either alefacept or efalizumab (Table 5).

A separate review examined the impact of clinical efficacy on cost of therapy per unit of clinical benefit over 6 months in patients with psoriasis. In this report, PASI 75 scores achieved with the recommended doses of alefacept, efalizumab, and etanercept were compared with the estimated annual cost of therapy (acquisition costs only using AWP pricing). This analysis revealed that the average annual cost of etanercept, even when 50 mg was administered twice a week, was $13,383 less than efalizumab therapy and $25,576 less than alefacept (Figure 2). Greater cost differences were noted when etanercept was dosed at 25 mg biweekly.

The same review estimated the relative 6-month costs of adverse reactions associated with alefacept, efalizumab, and etanercept. The review used the types and frequencies of adverse reactions from published placebo-controlled clinical trials and referenced direct medical cost estimates for treating the adverse reactions (Table 6).

### Summary

The overall cost of therapy for treating moderate to severe psoriasis is dependent on the acquisition costs, clinical effectiveness, safety, and patient tolerability of the product. Based on the currently available data, etanercept appears to offer a balance of efficacy with affordability for the treatment of moderate to severe psoriasis. Continued analysis of the relative merits of the biologics for the treatment of psoriasis should be performed as more established efficacy, safety, and utilization data becomes available. It should be noted that, at the time this article was written, etanercept had not been approved by the U.S. Food and Drug Administration for the treatment of psoriasis.

### Case Study 4. Absence of a Clear Therapeutic Difference: Multiple Sclerosis

There are 4 biologic drugs indicated for the treatment of relapsing-remitting multiple sclerosis (MS)—interferon beta-1a, interferon beta-1b, glatiramer, and mitoxantrone—yet none has been shown to be clearly superior to any other. In this case, the PA criteria developed for these biologics did not restrict coverage to a single...
drug as initial therapy because clear therapeutic differences have not been demonstrated among the available agents. MS is the most common acquired neurologic disease in young adults, affecting 400,000 Americans. Twice as many women as men are diagnosed with MS. The initial symptoms occur between 20 and 40 years of age. MS has a significant impact on health, quality of life, productivity, and employment. Only 20% of patients with MS have no discernible disability, 30% have intermittent symptoms, 40% have a slow progression of the disease, and 50% have cognitive impairment. Annual direct and indirect costs associated with the disease are estimated to be $2.5 billion.

Currently, no well-controlled comparative clinical trials have been conducted between the available biologic drugs. However, there may be some differentiation among the products based on indications. For example, mitoxantrone is reserved for patients failing other therapies for relapsing-remitting disease, and low-dose interferon-beta-1a is approved for attenuation of progression of MS following an initial event. Additionally, each drug possesses slightly different adverse reaction profiles, the potential for the development of transient neutralizing antibodies, dosing frequency, packaging, and cost.

In open-label trials, data has been generated that suggests interferon-beta-1b and glatiramer are superior to low-dose interferon-beta-1a in reducing the frequency of relapses. In the only direct comparative trial in relapsing-remitting MS, high-dose interferon-beta-1a was superior to low-dose interferon-beta-1a over a period of 1 year, and this difference was maintained through the second year of the trial.

At the time of Health Net’s review, there was very little difference in the net cost of the 3 interferon products or glatiramer. The absence of clinical evidence to support the choice of a preferred agent in this class led Health Net of Arizona to create PA criteria that allowed physicians to choose low-dose interferon-beta-1a, interferon-beta-1b, or glatiramer as the initial agent for relapsing-remitting MS. Mitoxantrone was reserved for patients with relapsing-remitting MS that progressed during therapy with one of the other agents.

Summary

In the absence of data supporting clear clinical, safety, or cost differences, PA criteria can be created that allow for a number of initial therapies. This provides physicians and members the ability to choose a drug based on secondary considerations such as dosing route and frequency. Covering multiple drugs when possible should result in increased patient and physician satisfaction.

Conclusion

Because of the rapid increase in the number of biologic agents and the lack of head-to-head trials, determining the clinical superiority of one agent for a specific condition may be challenging. This challenge is compounded by the need to ensure patient access to these innovative products while simultaneously managing costs. In order to assist pharmacy and medical decision makers in overcoming these obstacles, case studies were presented to illustrate how one commercial health plan evaluated and prioritized the available biologic agents for the treatment of RA, asthma, psoriasis, and MS. The cases use the available evidence to demonstrate that differences in drug efficacy, safety, tolerability, administration, distribution, and need for cotherapy affect the overall cost of therapy. As biologic agents become more commonly available, pharmacy decision makers must continually evaluate the evidence to determine therapies that provide the greatest clinical and economic value.

DISCLOSURES

Author Robert J. Lipsy received an honorarium from Amgen Inc. and Wyeth Pharmaceuticals, Inc., for participation in the symposium upon which this article is based. He is a consultant to Amgen Inc.

REFERENCES

Injectable Biologic Case Studies


Continuing Education

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

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Address: ______________________________

City: ________________________________  State: ________________  ZIP: _____________

Daytime phone: _________________________  Social Security #: ____________________

Fax number: ___________________________  E-mail: ____________________________

Member Type:  ☐ Active  ☐ Supporting Associate  ☐ Student  ☐ Nonmember

Posttest Answers:

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The Postgraduate Institute for Medicine is approved by the American Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. A total of .125 CEUs (1.25 contact hours) will be awarded to pharmacists for successful completion of this continuing education program. Successful completion is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. Continuing education statements will be mailed to pharmacists within 3 weeks of receipt of the Record of Completion, Posttest, and Program Evaluation forms. Universal Program No. 809-999-04-010-H01 (expiration date: 5/1/05). There is no fee for completing this educational activity.
Please indicate the correct answers on the Record of Completion.

1. Which of the following is not a basis for the classification of biologic agents?
   a. Molecular structure
   b. Mode of metabolism by the body
   c. Physical size
   d. Manufacturing process

2. Injectable therapies cost an estimated 10 times more than orally administered pharmaceuticals.
   a. True
   b. False

3. All of the following represent a potential impact of biologic agents on managed care organizations except
   a. a shift of biologic drug administration from inpatient to outpatient venues.
   b. reallocation of costs from the medical to the pharmacy budget.
   c. changes in drug distribution channels.
   d. all the above represent a potential impact

4. Effective management of utilization and costs for biologic agents requires
   a. appropriate data collection and analysis systems.
   b. evidence-based treatment guidelines.
   c. integrated pharmacy and medical claims databases.
   d. all the above

5. Which of the following is not an example of cost shifting?
   a. Requiring prior authorization
   b. Increasing copays
   c. Creating an injectable insurance rider
   d. Adding coinsurance

6. Who among the following health care providers has a potential financial incentive to prescribe agents requiring intravenous infusion?
   a. Physicians working with capitated agreements
   b. Physicians working in a fee-for-service environment
   c. Pharmacists working with a specialty pharmacy service
   d. None of the above has a potential financial incentive to prescribe agents requiring intravenous infusion

7. Centers for Medicare and Medicaid Services (CMS) coverage decisions are
   a. prompted by Congress.
   b. based on the professional opinion of experts.
   c. conducted on either a local or national level.
   d. driven primarily by cost.

8. For CMS reimbursement, a biologic agent must
   a. have an FDA indication for the disease under consideration.
   b. provide a significant cost savings over existing therapies.
   c. be deemed to be reasonable and necessary for the treatment of a given condition.
   d. all the above

9. The NCQA Health Plan Employer Data and Information Set (HEDIS) consist of a series of measures used to assess several aspects of the clinical effectiveness of a product or procedure including
   a. relevance.
   b. soundness.
   c. feasibility.
   d. all the above

10. Evidence published by Fisher et al. suggests that regional variations in health care spending were primarily accounted for by widespread use of discretionary medical services.
    a. True
    b. False

11. Strategies that can be used to evaluate biologic agents include
    a. examining the total cost of therapy.
    b. comparing achieved clinical outcomes with cost of therapy.
    c. both a and b
    d. neither a nor b

12. Which of the following patient characteristics should be taken into account when considering biologic therapy?
    a. Willingness to participate in therapy
    b. Ability to pay for therapy
    c. Patient’s teachability
    d. All the above must be considered
Anticipating the Future: How the Emergence of Innovative Biologic Agents Impacts Benefit Design, Utilization, and Provider Relations

Participant’s name: _____________________________ Date: ______________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

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<th>Scale For Questions 5 and 6</th>
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<tr>
<td>1 = Not at all</td>
<td>1 = Poor</td>
</tr>
<tr>
<td>2 = Not very well</td>
<td>2 = Fair</td>
</tr>
<tr>
<td>3 = Somewhat well</td>
<td>3 = Good</td>
</tr>
<tr>
<td>4 = Well</td>
<td>4 = Very good</td>
</tr>
<tr>
<td>5 = Very well</td>
<td>5 = Excellent</td>
</tr>
</tbody>
</table>

Using the scale above for questions 1-4, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objectives:
1. discuss the impact of treatment with biologics on benefit design, provider relations, and quality of care in Medicare and managed care; ___
2. identify how Medicare coverage decisions affect managed care and other payers and their formularies; ___
3. explain the rationale for cost shifting, multi-tiered copays, prior authorization, and use of specialty pharmacy services to manage costs associated with biologic drugs; ___
4. describe the effectiveness and long-term value of biologic agents in different disease states. ___

Using the scale above for questions 5 and 6, please indicate the number that best expresses your opinion.

5. What is your overall rating of this program? ___
6. How would you rate the pertinence of this program material to your practice? ___
7. To what degree was there promotional bias? (check one) 
   a. Not at all ___
   b. Somewhat ___
   c. A great deal ___
8. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)  
   1 No change  2 3 4 5 Significant change
9. Please indicate the length of time it took to complete this program. (circle selection (s))  
   Hours: 1 2 3  
   Minutes: 0 15 30 45
10. Please rate the difficulty factor for completing this CE program. (circle selection)  
    Easy Moderate Difficult
11. Please rate your willingness to recommend this program to colleagues. (circle selection)  
    Very willing Willing Not willing
12. Please indicate which venue you prefer for obtaining continuing education. (circle selection)  
    Written monograph Slides Videos Internet-based Live sessions Other: _____________________________