

## The Challenge of Integrating Monoclonal Antibodies into the Current Healthcare System

Diana I. Brixner, RPh, PhD; and Scott A. Bull, PharmD

### **Abstract**

Although there are few monoclonal antibody (MoAb) products on the market, the biotechnology industry has made considerable progress over the last decade. The industry has developed new technology to address the primary hurdles facing the development of MoAbs—including the immune response to murine-derived antibodies as well as lack of tumor specificity. As the techniques for development become more refined, more products will be approved by the Food and Drug Administration. Integrating these products into the existing healthcare system will be a challenge, given their high acquisition costs. Recent pharmacoeconomic examples outlined in this paper confirm that MoAb products will need to be supported with proven clinical and economic profiles. As long as a global clinical and economic perspective is taken and patient care benefits can be demonstrated, the place of MoAbs in the future of healthcare will be assured.

(*Am J Man Care* 1997;3:903-911)

In the cost-driven climate of the current healthcare system, it is possible that new technologies will not be fully exploited to the benefit of patients. During the past two decades, monoclonal antibody (MoAb) technology has had a major impact on the detection and management of the two leading causes of death in the United States—cardiovascular disease<sup>1</sup> and cancer.<sup>2,3</sup> Yet, some argue that we cannot afford to invest healthcare dollars in high-priced procedures or products.<sup>4</sup> This paper presents a brief overview of MoAb technology, including developmental tech-

niques and therapeutic challenges in their delivery, a review of products on the market, and a discussion of MoAb pharmacoeconomics.

### **Monoclonal Antibodies and Naked DNA Vaccines**

For many years, we have known that antibodies play a critical role in our defense against foreign objects, or antigens, that invade biological systems.<sup>5</sup> For a long time, synthetic antibodies could not be used to treat disease due to their lack of antigen specificity. In 1975, however, researchers developed a laboratory procedure for producing antigens with predetermined specificity, or hybridomas, by fusing normal antibody-producing B-lymphocytes with “immortal” myeloma cells.<sup>6</sup> As a result, hybridomas that secreted antibodies specific to one target site on an antigen, MoAbs, were isolated. This discovery initiated a cascade of development of MoAbs that deliver diagnostic and therapeutic agents to target sites.

More recently, recombinant deoxyribonucleic acid (DNA) techniques have allowed mass production of MoAbs. Thanks to these techniques, a gene that synthesizes a specific antibody can be constructed, inserted into a host cell for replication and expression, and then isolated. In addition, new libraries of DNA information now allow gene sequences that code for antibody peptides with high binding affinity for specific antigens to be quickly identified and cloned, resulting in mass production of MoAbs.<sup>7-10</sup>

Naked DNA vaccines—nucleic acid sequences (plasmid DNA) that code for the antigenic polypeptide in the host<sup>11</sup>—also hold significant disease-prevention potential. Unlike traditional vaccines, which consist of the whole pathogen or portions of the pathogen such as purified or recombinant proteins or synthetic peptides, naked DNA vaccines do not contain the actual antigen and do not induce an immune response.

Although naked DNA vaccines do not specifically produce monoclonal antibodies, they eliminate many

From Health Care Management, Novartis Pharmaceuticals, Summit, NJ.

Address correspondence to: Diana I. Brixner, RPh, PhD, Health Care Management, Novartis Pharmaceuticals, 556 Morris Avenue, Summit, NJ 07901.

of the typical therapeutic challenges associated with drug delivery such as human antimurine antibodies, poor biodistribution, and decreased potency. They are simple to prepare and produce, and they are highly stable relative to proteins and other biologic polymers. Although injection of plasmid DNA poses a risk of genomic integration, direct gene transfer has been proven to work safely in animals against a variety of antigens.<sup>12</sup> For these reasons, further research into naked DNA vaccines is warranted.

### Therapeutic Challenges

Although the development of MoAbs was founded on sound scientific principles, a number of fundamental problems hindered the clinical application of this technique. Since monoclonal antibodies are derived from mice, they produce an immunologic reaction in humans. Humans recognize the murine MoAb as foreign and produce human antimurine antibodies (HAMA) to it. HAMA can also affect the reliability of certain immunoassays and this could, in turn, lead to unnecessary clinical intervention.

HAMA formation and related adverse events can be minimized by administering smaller amounts of the murine protein.<sup>13</sup> Alternately, human MoAbs may be used, although they also pose difficulties when applied to the clinical setting. Human cells are less inclined to fuse than their murine counterparts, and this can lead to a low fusion frequency, low secretion levels, and chromosomal instability of the hybrids.<sup>14</sup> A technological compromise has been the development of the "chimeric" antibody, or a combination of the mouse variable region and the constant region of a human antibody. This helps to decrease the HAMA response, increase specificity, and improve some of the developmental problems associated with pure human antibodies.<sup>15</sup>

There is also a need to increase the effectiveness of antibody techniques and therapies. One approach to achieving this goal has been the development of "bifunctional" or "bispecific" antibodies, which are two distinct antibodies that are fused. Bifunctional antibodies that bind to a targeted tumor as well as a radiolabel may be useful for imaging. In this case, the antigen-specific portion of the antibody first binds to the targeted tumor antigen. Subsequently, the radiolabel specific to the second arm of the antibody is injected, thereby permitting imaging of the tumor.<sup>16</sup> This technology may also help to increase an antibody's disease-fighting capability, as both arms can be antigen-specific. This may strengthen tumor antigen binding and may maximize the immune response to the tumor.<sup>17</sup>

Tumor cell heterogeneity presents another therapeutic challenge. Attempts have been made to reduce this heterogeneity with bioresponse modifiers, such as interferons, which increase the expression of tumor-specific antigens by tumor cells.<sup>18</sup> Another novel approach is the use of avidin (or streptavidin) and biotin, both which can be conjugated to a targeted monoclonal antibody. One can be conjugated to nontumor-bound antibodies and administered. After this clears from normal tissue, the appropriate therapeutic or diagnostic conjugate of the other molecule can be administered and targeted directly to the site of the antigen.<sup>19</sup>

MoAbs are also large, cumbersome molecules with poor pharmacokinetic profiles; they have a slow onset of action and a prolonged clearance rate. These characteristics can increase the potential for adverse events. The most effective approach to these issues has been enzymatic breakdown of the antibody into smaller fragments that still contain the binding site. The smallest component to date has been the single chain fragment (sFv), which has excellent solubility and superior pharmacokinetic and biodistribution profiles. Further, the sFv fragments have also demonstrated a potential to penetrate solid tumors—previously a limited target for MoAbs.<sup>20</sup>

These advancements in the delivery of monoclonal antibodies have led several companies to initiate full-scale production of biologically active MoAbs. MoAbs that target specific antigens can aid in the diagnosis and treatment of various oncological tumor types, block the effects of gram negative endotoxins, prevent organ rejection, decrease platelet aggregation, and reverse drug toxicity. As research in this area continues, and production becomes more efficient, MoAbs will likely play a significant role in disease treatment.

### Biotechnology Marketplace Overview

Despite the challenges of clinical application, production, and product licensing, a number of MoAb-derived products have reached the marketplace. According to one recent survey, more than 100 biotechnology medicines and vaccines are in human clinical trials or are awaiting Food and Drug Administration (FDA) approval.

Table 1 list all MoAbs currently in phase III clinical development. These products are testimony to the growing interest in molecular biology and biotechnology by pharmaceutical firms. In fact, the proportion of biotechnology research performed by major pharmaceutical firms rose from 2% in 1980

**Table 1.** Monoclonal Antibody Products in Phase III Development

Product Name	Originator	License Company	Type of Monoclonal Antibody	Therapy Description
inolimomab enllimomab	Biotest Boehringer Ingelheim	ISIS Pharmaceuticals	Biotechnology Derived Murine	Immunosuppressant Anti-asthma immunosuppressant Anti-arthritic, Immunological Vulnerary Neuroprotective
nebacumab	Centocor	Takeda Nihon Seiyaku	Human	Septic shock treatment immunomodulator, anti-infective
Bay-x-1351	Chiron	Bayer Celltech	Biotechnology Derived	Septic shock treatment
IDEC-C2B8	IDEC	Genentech Zenyaku Kogyo Roche	Chimeric	Anti-cancer, immunological
IDEC-CE9 1	IDEC	SmithKline Beecham	Chimeric	Anti-arthritic, immunological Anti-asthma Immunosuppressant
MAK-195F	Knoll		Murine	Monoclonal antibody, murine Septic shock treatment
Medi-493	Medimmune		Chimeric	Immunomodulator, anti-infective
T10B9	Medimmune	BioTransplant	Murine	Immunosuppressant Anti-cancer, immunological Monoclonal antibody, chimeric
HNK-20	OraVax	CSL	Biotechnology Derived	Anti-viral, other
odulimomab	Pasteur Merieux		Murine	Immunosuppressant
dacliximab	Protein Design Labs	Roche	Chimeric	Anti-arthritic, immunological Immunosuppressant Anti-cancer, immunological Ophthalmological Anti-psoriasis
HuM195 MAb Protein Design	Protein Design Labs	Kanebo	Chimeric	Anti-cancer, immunological
sevirumab	Protein Design Labs	Boehringer Mannheim	Human	Immunomodulator, anti-infective Ophthalmological
SB-209763	Scotgen	SmithKline Beecham	Chimeric	Anti-viral, other
LYM-1	Techniclone	Green Cross Biotechnology Development Corp	Biotechnology Derived	Anti-cancer, immunological Diagnosis

Adapted from Pharmaprojects<sup>42</sup>

to 33% in 1993. As a result, there are increasingly fewer distinctions between pharmaceutical and specialized biotechnology companies.<sup>21</sup>

Figure 1 shows a breakdown of the biotechnology industry by market segment. More than two thirds of all research has been performed for therapeutic or

diagnostic products, with therapeutic products alone representing nearly half of all research and development work.<sup>22</sup> For this review of products on the market and in development, we selected products that either demonstrate the diverse indications for MoAbs or that have been subjected to pharmacoeconomic analysis.

*Therapeutic products.* Although human studies showed promise for digoxin immune FAB and related antiserum products as early as 1976,<sup>23</sup> the first therapeutic application of true MoAb technology was not approved until 1993. The first MoAb product was muromonab-CD3, or OKT3, an immunosuppressant drug. This is a murine monoclonal antibody that reacts to a surface antigen of mature human T-cells that is vital to their function.<sup>24</sup> OKT3 was initially indicated only for prevention of renal transplant rejection, and studies have shown that adding OKT3 to traditional induction therapy during kidney transplantation can decrease the number of rejection episodes and delay time to graft failure.<sup>25,26</sup> OKT3 is also now indicated for use in heart and liver transplants.

In addition to the prevention of organ transplant rejection, MoAbs have been researched extensively for the treatment of sepsis. HA-1A is one such product. In the first clinical trial involving this anti-endotoxin, only patients with confirmed gram-negative sepsis showed any benefit.<sup>27</sup> Unfortunately, sepsis progresses rapidly and requires treatment before blood results can identify those patients who may

qualify for treatment. A second, FDA-requested clinical trial was subsequently suspended due to excess mortality in HA-1A-treated patients, although analysis of the data confirmed that gram-negative bacteremic patients with shock benefitted from treatment.<sup>28</sup> In the absence of clear benefit, universal HA-1A treatment for all patients with potential gram-negative bacteremia would create a significant economic burden on the hospital and patient.<sup>29</sup> The cost-effectiveness of HA-1A has been evaluated extensively, and these data are reviewed later in this paper.

In 1994, the FDA approved abciximab as an adjunct to percutaneous transluminal coronary angioplasty (PTCA) or atherectomy, to help prevent acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel.<sup>30</sup> This product is a fragment of the chimeric human-murine MoAb 7E3, which inhibits platelet aggregation by binding to the glycoprotein IIb/IIIa receptor of human platelets.

*Diagnostic products.* A number of diagnostic products have reached the market. The first radiolabeled MoAbs for use in the diagnosis of ovarian and colorectal cancer were launched in 1992, and the manufacturer of these products is also exploring diagnostic agents for breast and lung cancer.

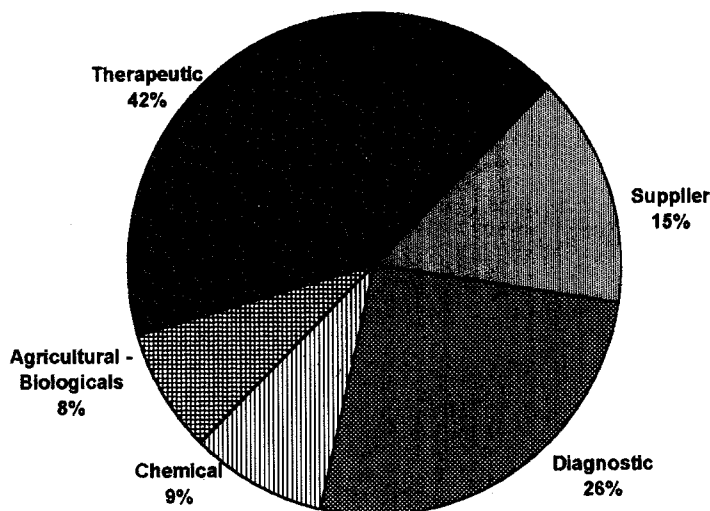
Indium III murine monoclonal antibody FAB to myosin (Myoscint) is another diagnostic product developed to detect and locate tissue damage resulting from heart attack.<sup>31</sup> When myocardial cells die, their protein (myosin) becomes exposed. Myoscint, a radio-isotope-labeled antibody, binds to exposed myosin, which can then be imaged with a gamma camera.

Another diagnostic agent is a fibrin-specific antibody for blood clot imaging.<sup>21</sup>

### Are MoAbs Cost-Effective?

Initially, most biotechnology firms assumed that a novel new class of compounds like MoAbs would demand a premium price. However, with the arrival of

**Figure 1.** The Biotechnology Industry Broken Down by Market Segment.



Adapted from Lee and Burill<sup>22</sup>

cost containment, managed care, and integrated healthcare systems, the environment for introducing any new product has been dramatically changed. Manufacturers of high-priced agents must now justify cost by demonstrating overall value to the healthcare system. This implies that valid economic and outcomes data should be used to compare incremental differences in outcomes to incremental differences in cost.

Unfortunately, because of their complex development process, MoAbs are currently very expensive to produce. Essentially, the production process can be broken down into three steps: preparation and validation of the cell stocks to be used, reproduction and efficient transfer of cells to the bioreactor, and MoAb recovery with minimal contamination from cell debris and media contamination.<sup>15</sup> MoAbs are often derived through recombinant DNA techniques using phage display libraries, and they ultimately require large-scale fermentation. Because of the complex nature of these proteins, characterization is also much more difficult than for small organic compounds. In the future, however, production costs are likely to decline as manufacturing techniques become standardized.

Nevertheless, it is essential to weigh the cost of these products in relation to their impact on the overall cost of the treatment or procedure for which they are indicated, as they can ultimately reduce costs. For example, Blue Cross of Western Pennsylvania found that peripheral blood stem cell transplantation and filgrastim (colony stimulating factor) therapy, an expensive biotechnology product-based therapy, improved survival rates and reduced costs associated with bone marrow transplants by 50% since 1990.<sup>32</sup> Bone marrow transplantation is one of the most expensive treatments available for cancer, costing an average of \$193,000 per patient.<sup>33</sup> This example demonstrates that clinical experience, coupled with updated treatment

protocols, can improve patient outcomes while decreasing overall healthcare costs. Over time, MoAbs may play a similar role.

### Pharmacoeconomic Examples

Several pharmacoeconomic examples follow.

*OKT3 for kidney transplantation induction therapy.* At first glance, the addition of OKT3 to the traditional induction therapy regimen used during kidney transplantation appears expensive. The average wholesale price is \$522 per 5 mg bottle, and at least 10 days of OKT3 therapy are required. The need for drug monitoring and an increased risk of infection due to OKT3 further increases treatment costs. One recent pharmacoeconomic study<sup>34</sup> showed that the addition of OKT3 to the induction regimen cost an additional \$8,219 per patient and saved \$5,915 per patient due to a reduction in the incidence of graft rejections. Although these savings did not initially outweigh the cost of OKT3, the cost-effectiveness of the product improves with time. Table 2 compares the cost-effectiveness of OKT3 and traditional therapy with traditional therapy only. Based on the assumption that if each year of extended graft survival prevents an equal amount of patient time on renal dialysis, the study investigators concluded that OKT3 provides sufficient benefit to offset its additional cost.

*HA-1A for sepsis treatment.* The cost of this MoAb for sepsis treatment has been examined using several

**Table 2.** Incremental Cost to Extend Graft Survival Over 1 Year, 5 Years, and Lifetime of Graft

Years of Graft Survival	With Monoclonal Antibody (OKT3)	Without MOAb	Incremental Cost Difference
<b>1 Year</b>			
No. of grafts surviving	90	82	8
Costs	\$9,176,671	\$8,979,400	\$197,000
Cost-effectiveness ratio	\$98,671	\$105,640	\$24,625
<b>5 years</b>			
No. of grafts surviving	73	64	9
Costs	\$11,244,800	\$10,852,100	\$392,200
Cost-effectiveness ratio	\$30,474	\$32,687	\$10,614
<b>Until end of graft survival</b>			
Total years of graft survival	741	635	106
Costs	\$14,412,100	\$13,528,600	\$883,500
Cost-effectiveness ratio	\$19,450	\$21,305	\$8,335

Adapted from Shield et al<sup>34</sup>

cost models. A simple cost model in which only two outcomes, death and survival, were considered showed that adding HA-1A to standard regimens for treating sepsis increased overall hospital charges per patient, although the total additional charges were less than the increased cost of the agent itself.<sup>35</sup> In the analysis, based on average results of two separate clinical trials,<sup>36,37</sup> the anti-endotoxin MoAb was expected to increase survival by 8% in patients with confirmed gram-negative sepsis over conventional therapy.

When various probabilities and charges were applied to a decision analysis model, billed charges per patient varied from \$38,304 to \$52,182 when \$3,000 was used as the cost of the agent (acquisition cost) (Figure 2). By applying different acquisition costs to the model, the researchers concluded that no additional charges when the MoAb is added to the standard treatment regimen, provided the agent cost is \$870 (Figure 3). Below this price, a patient would accrue fewer charges than a patient on standard antibiotic therapy alone.

*Abciximab.* Upon the launch of this product, a cost-effective analysis had been completed based on the Evaluation of c7E3 to Prevent Ischemic Complications

trial.<sup>38</sup> Based on these analyses,<sup>39,40</sup> eight additional patients out of 100 were event-free due to 6 months of treatment with abciximab, yielding \$110,000 in reduced hospital costs and doctor visits, equivalent to \$1,100 per patient. An additional \$500 savings was lost due to medical costs from increases in bleeding associated with abciximab therapy. In this trial, the following occurrences were considered as "events": death, nonfatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, unplanned implantation of a coronary stent, or insertion of an intra-aortic balloon pump for refractory ischemia.<sup>38</sup>

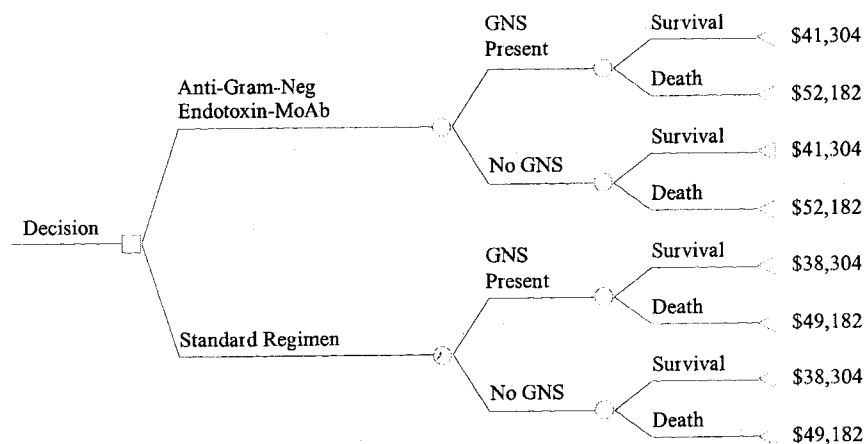
In the United States, a net wholesale price of \$450 per vial would cost the average patient using 3 vials \$1,350. With appropriate discounting, the price may be brought down to \$1,150 per patient.<sup>39,40</sup> As more clinical experience is gained, other factors may influence its cost-effectiveness. Reductions in heparin and aspirin doses may be possible in abciximab-treated patients, potentially decreasing the incidence and severity of bleeding complications. The product may also offer substantially higher cost

savings in certain patient populations, as abciximab therapy has been associated with a decreased need for revascularization in high-risk patients.<sup>41</sup> A resultant reduction in the need for surgery and prevention of angina pain should also reduce morbidity, thereby further improving the product's cost-effectiveness as well as patients' quality of life.<sup>41</sup>

### Integration of MoAbs Into A Cost-Driven Healthcare System

Without pharmacoeconomic information, it is difficult to integrate MoAbs into current clinical practice. Although clinical

**Figure 2.** A Decision Analysis Model for the Use of Anti-Gram-Negative Endotoxin MoAb in the Treatment of Gram-Negative Sepsis



The square indicates a decision node and the circles indicate chance nodes. Model used hospital charges (not costs) obtained from records of 1,405 patients with International Classification of Diseases, 9th rev code for sepsis. Adapted from Chalfin et al<sup>35</sup>

data may support the efficacy of products and provide guidance on appropriate indications, the decision to use MoAbs remains that of the provider and is often influenced by healthcare administrators.

When different therapeutic options provide similar efficacy endpoints or outcomes, various other characteristics such as dosing schedule or side effect profile may become important. Many of these factors can be examined in a sound pharmacoeconomic analysis. For example, drugs dosed numerous times per day may cost more in terms of pharmacy preparation and nursing administration time than once-daily agents. The side effect profile of an agent can also affect overall costs significantly, as some side effects may require expensive concomitant medications, may complicate comorbid conditions, or may require additional treatment. Route of administration may also provide important insight into an agent's cost-effectiveness. For example, a patient may need to extend a hospital stay if a drug is only available intravenously. Finally, appropriate utilization of a product can also affect overall costs. When a therapy is used in populations from which only a small group of patients will benefit, the average cost per patient increases. On the other hand, if the appropriate population of patients can be identified and targeted, the cost of successful treatment can be substantially decreased.

Pharmaceutical companies must consider all perspectives—including that of the payor—when setting the price of a pharmaceutical product. For example, in an institutional setting, a pharmacist in charge of a drug budget may be reluctant to accept a high-priced MoAb on the formulary. However, the hospital administrator can provide a more global institutional perspective, and a physician representative can provide an overall clinical perspective that may broaden the dimensions of decision-making. As hospitals become part of integrated healthcare delivery systems, the impact of new technologies on total

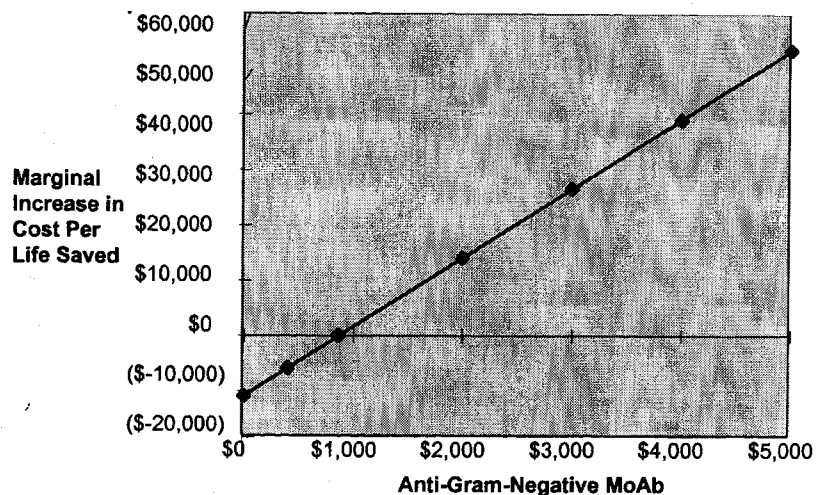
episodes of care will become even more relevant. Likewise, in a staff- or group-model managed care system, all caregivers take a personal and financial interest in keeping down the overall healthcare costs.

In systems in which sections of healthcare management are "carved out," the perspectives on component costs may be very different. For example, a capitated pharmacy operating in a non-integrated healthcare system may be reluctant to accept premium priced drug therapy, even if it decreases physician visits and lab tests. Such a situation could delay acceptance of high-cost therapies by drug formularies. This may pose a particular challenge for MoAbs since MoAb therapy is often directed to cancer therapy, and cancer care is sometimes "carved-out" of traditional health benefits.

### Summary and Conclusions

Despite the relative paucity of MoAb products in

**Figure 3.** Sensitivity Analysis of Anti-Gram-Negative Endotoxin MoAb Acquisition Cost.



Cost per additional life saved was based on an increased survival rate of 8% in the anti-gram negative endotoxin MoAb treatment arm. Produced from data by Chalfin et al.<sup>35</sup>

the marketplace, the biotechnology industry has made considerable progress over the last decade. Improved technology has addressed the principal hurdles facing the development of MoAbs—including the immune response to murine-derived antibodies as well as lack of tumor specificity. As the techniques for development become more refined, more products will be approved by the FDA.

Recent pharmacoeconomic examples confirm that MoAb products will need to come to market with proven clinical and economic profiles. Still, integration of these products into the existing healthcare system will be challenging, given their high acquisition costs. To assure the survival of these potentially invaluable products, overall cost-effectiveness of them must be demonstrated. As long as a global clinical and economic perspective is taken and patient care benefits can be demonstrated, the place of MoAbs in the future of healthcare should be assured.

... REFERENCES ...

1. Fareed J, Hoppensteadt D, Iyer L, et al. Impact of biotechnology in the diagnostic and therapeutic management of cardiovascular disorders. In: Longenecker JB, et al, eds *Nutrition and Biotechnology in Heart Disease and Cancer*. New York, NY: Plenum Press; 1995:99-110.
2. Kuhn JA, Thomas G. Monoclonal antibodies and colorectal carcinoma: A clinical review of diagnostic applications. *Cancer Invest* 1994;12:314-323.
3. Divgi CR. Status of radiolabeled monoclonal antibodies for diagnosis and therapy of cancer. *Oncology* 1996;10:939-958.
4. Ubel PA. Can we continue to afford organ transplants in an era of managed care? *Am J Man Care* 1996;2:293-297.
5. Kasper DL. Introduction to bacterial diseases. In: Mandell GL, et al, eds. *Principles and Practice of Infectious Diseases*. New York, NY: Wiley; 1990:1484-1489.
6. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975;256:495-497.
7. Merz CD, Dunn RJ, Drapeau P. Generating a phage display antibody library against an identified neuron. *J Neurosci Methods* 1995;62:213-219.
8. Tyutyulkova S, Paul S. Selection of functional human immunoglobulin light chains from a phage-display library. *Appl Biochem and Biotechnol* 1994;47:191-198.
9. Jacobsson K, Frykberg L. Cloning of ligand-binding domains of bacterial receptors by phage display. *BioTechniques* 1995;18:878-885.
10. Huse WD, Sastry L, Iverson SA, et al. Generation of a large combinatorial library of the immunoglobulin repertoire in phage lambda. *Science* 1989;246:1275-1281.
11. Pardoll DM, Beckerleg AM. Exposing the immunology of naked DNA vaccines. *Immunity* 1995;3:166-169.
12. Heather LD, Michel ML, Whalen RG. Use of plasmid DNA for direct gene transfer and immunization. *Ann NY Acad Sci* 1995:21-29.
13. Reynold JC, Del Vecchio S, Sakahara H, et al. Anti-murine antibody response to mouse monoclonal antibodies: Clinical findings and implications. *Med Biol Int J Radiat Appl Instrum B* 1989;16:121-125.
14. Mally M. Genetic engineering in human lymphocytes for the production of monoclonal antibodies. *Hum Antibody Hybridomas* 1990;1:27-33.
15. Brixner D. Monoclonal antibodies: From the research lab to the pharmacy. *Pharm Pract* 1991;4:94-102.
16. Goodwin DA, Meares CF, McCall MJ, et al. Pre-targeted immunoscintigraphy of murine tumors with indium-111-labeled bifunctional hapten. *J Nucl Med* 1988;29:226-234.
17. Henderson C. New clinical trials spark antibody renaissance. *Cancer Researcher Weekly* 1994:15.
18. Fisher PB, Rowley PT. Regulation of growth, differentiation and antigen expression in human tumor cells by recombinant cytokines: Applications for the differentiation therapy of human cancer. In: Waxman S, Rossi GB, Takaku F, eds. *The Status of Differentiation Therapy of Cancer*. Vol 2. New York, NY: Raven Press; 1991;2:201-214.
19. Paganelli G, Magnani P, Zito F, et al. Three-step monoclonal antibody tumor targeting in carcinoembryonic antigen-positive patients. *Cancer Res* 1991;51:5960-5966.
20. Anonymous. Is there a small answer to Mabs' big problems? *The Genesis Report/Rx* 1994;4:33-38.
21. Mossinghoff G. A 1993 Survey of 143 biotechnology medicines in testing. In: *Development - Biotechnology Medicines*. Washington, DC: Pharmaceutical Manufacturers Association; 1993:1-11.
22. Lee KB, Burrill GS. *Biotechnology 95: Reform, Restructure, Renewal*. Ninth Annual Report on Biotechnology Industry. New York, NY: Ernst & Young; 1994:52.
23. Smith TW, Haber E, Yeatman L, et al. Reversal of advanced digoxin intoxication with fab fragments of digoxin-specific antibodies. *N Engl J Med* 1976;294(15):797-800.
24. Ortho Multicenter Transplant Study Group. A randomized clinical trial of OKT3 monoclonal antibodies for acute rejection of cadaveric renal transplants. *N Engl J Med* 1985;313:338-342.
25. Abramowicz DJ, Goldman M, DePauw L, et al. The long-term effects of prophylactic OKT3 monoclonal antibody in cadaver kidney transplantation: A single-center, prospective, randomized study. *Transplantation* 1992;54:433-437.
26. Norman DJ, Kahana L, Shield CF, et al. A randomized clinical trial of induction therapy with OKT3 in kidney transplantation. *Transplantation* 1993;55:44-50.
27. Ziegler EJ, Fisher CJ, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. *N Engl J Med* 1991;324:429-436.
28. Luce JM. Introduction of new technology into critical care practice: A history of HA-1A human monoclonal antibody against endotoxin. *Crit Care Med* 1993;21:1233-1241.
29. Bates DW, Lee TH. Projected impact of monoclonal anti-endotoxin antibody therapy. *Arch Intern Med* 1994;154:1241-1249.
30. Califf R. Use of monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-961.
31. Anonymous. Nuclear medicine workload to increase. *Health Technology Trends* 1993;5:1-6.



32. Lawless GD. Cost-effectiveness of autologous bone marrow transplantation. *Am J Health-Syst Pharm* 1995;52(S19):S11-S14.
33. Westerman IL, Bennett CL. A review of the costs, cost-effectiveness and third-party charges of bone marrow transplantations. *Stem Cells* 1996;4(3):312-319.
34. Shield CF, Jacobs JR, Wyant S, et al. A cost-effectiveness analysis of OKT induction therapy in cadaveric kidney transplantation. *Am J of Kidney Dis* 1996;27:855-864.
35. Chalfin DB, Holbein EB, Fein AM, Carlon GC. Cost-effectiveness of monoclonal antibodies to gram-negative endotoxin in the treatment of gram-negative sepsis in ICU patients. *JAMA* 1993;269:249-254.
36. Schulman, KA, Glick HA, Rubin H, et al. Cost-effectiveness of HA-1A monoclonal antibody for gram-negative sepsis. *JAMA* 1991;266:3466-3471.
37. Greenman RL, Schein RMH, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. *JAMA* 1991;266:1097-1102.
38. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; 330:956-961.
39. Cost-effectiveness of ReoPro. *SCRIP* 1994; December 6(1981):24.
40. First launches of ReoPro. *SCRIP* 1995; February 17(2000):21.
41. Faulds D, Sorkin EM. Abciximab (c7E3 Fab): A review of its pharmacology and therapeutic potential in ischemic heart disease. *Drugs* 1994;48:583-598.
42. Pharmaprojects (vol 17). Richmond, Surrey, UK: PJB Publications 1997.