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Perspective

mAbs

A business perspective

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Abbreviations: AA, allergic asthma; AS, ankylosing spondylitis; AC, angioplasty complications; AMD, age-related macular degeneration; AML, acute myelogenous leukemia; AS, ankylosing spondylitis; BC, breast cancer; BD, behcet's disease; BLA, biological license application; CD, Crohn disease; CHF, congestive heart failure; CI, cardiac ischemia; CLL, chronic lymphocytic leukemia; CO, colitis; CRC, colorectal cancer; DLBC, diffuse large B-cell lymphoma; DMARD, disease-modifying anti-rheumatic drugs; EGFR, epidermal growth factor receptor; F-RSV, fusion protein of RSV; IND, investigational new drug; JIA, juvenile idiopathic arthritis; mCRC, metastatic colorectal cancer; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; OR, organ rejection; ORR, oncology overall response rate; OS, oncology overall survival clinical endpoint; P, pediatric; PA, psoriatic arthritis; PFS, oncology progression-free survival; PP, plaque psoriasis; PS, psoriasis; PNH, paroxysmal nocturnal hemoglobinuria; PTCA, percutaneous transluminal coronary angioplasty; RA, rheumatoid arthritis; RCC, renal cell carcinoma; RSV, respiratory syncytial virus; SCCHN, squamous cell carcinoma of the head and neck; TNF, tumor necrosis factor; UC, ulcerative colitis; VEGF, vascular endothelial growth factor

Key words: autoimmune, biosimilars, buy and bill, comparative trials, drug approval, monoclonal, oncology, reimbursement

The twenty two monoclonal antibodies (mAbs) currently marketed in the U.S. have captured almost half of the top-20 U.S. therapeutic biotechnology sales for 2007. Eight of these products have annual sales each of more than $1 B, were developed in the relatively short average period of six years, qualified for FDA programs designed to accelerate drug approval, and their cost has been reimbursed liberally by payers. With growth of the product class driven primarily by advancements in protein engineering and the low probability of generic threats, mAbs are now the largest class of biological therapies under development. The high cost of these drugs and the lack of generic competition conflict with a financially stressed health system, setting reimbursement by payers as the major limiting factor to growth. Advances in mAb engineering are likely to result in more effective mAb drugs and an expansion of the therapeutic indications covered by the class. The parallel development of biomarkers for identifying the patient subpopulations most likely to respond to treatment may lead to a more cost-effective use of these drugs. To achieve the success of the current top-tier mAbs, companies developing new mAb products must adapt to a significantly more challenging commercial environment.

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Introduction

Monoclonal antibodies have captured eight of the top 20 spots for best selling biotechnology drugs in 2007 (Table 1), have a sales growth rate of >35%, compared to <8% for small-molecule drugs[1] and they now constitute the largest single class of biological drugs under development.[2]

The commercial success of mAbs has attracted significant investment in research and development by both industry and academia, and in turn this has resulted in notable gains in the ability to engineer mAbs to address deficiencies of current products and to enter new therapeutic areas. The field, however, faces reimbursement barriers resulting from the high cost of these drugs. In this article we analyze the development and characterization of approved mAbs in the context of the regulatory and economic landscape facing new mAb products.

Markets and Therapeutic Indications

Currently, 22 mAbs approved by the FDA are actively commercialized (Table 1). If one accepts a threshold for indisputable business success at $1 B in annual sales, eight of these mAbs can be placed in a first tier that accounts for almost $25 B in sales, or about half of the 2007 top-20 annual biotechnology sales. The remaining 14 mAbs can be grouped into a second tier that accounts for slightly over $2 B in sales.

Three of the First Tier mAbs are for oncology indications (trastuzumab, bevacizumab and cetuximab), two for autoimmune diseases (infliximab and adalimumab), one for both oncology and autoimmune indications (rituximab), and the remaining two for specialized indications such as age-related macular degeneration

Table 1 **FDA-approved marketed mAbs**

Name		Structure	Target	Indication		Path	Approval (Y)	Sales	% Top 20
Generic	Trade			Landing	Expansion				
First Tier								**(U.S. $B)**	
infliximab	Remicade®	Ch	TNF	CD	RA AS PA UC PP	O, A, P, F	4.6	$5.0	9.84
rituximab	Rituxan®, MabThera®	Ch	CD20	NHL	RA DLBC 1-NHL	O, P	5.1	$4.9	9.62
trastuzumab	Herceptin®	Hm	HER2	mBC	BC	F, P	7.5	$4.3	8.45
bevacizumab	Avastin®	Hm	VEGF	mCRC	mCRC NSCLC HER2- BC[a]	F, P	7.1	$3.6	7.15
adalimumab	Humira®	Hu	TNF	RA	RA JIA PA AS CD PP	O	3.7	$3.1	6.04
cetuximab	Erbitux®	Ch	EGFR	mCRC	SCCHN	A, P	9.7	$1.4	2.73
ranibizumab	Lucentis®	Hm	VEGF	AMD		P	6.8	$1.2	2.39
palivizumab	Synagis®	Hm	RSV	RSV		P	3.6	$1.1	2.25
Second Tier								**(U.S. $M)**	
tositumomab	Bexxar®	Mu	CD20	NHL[b]	NHL[c]		13.7	$10.3	0.02
alemtuzumab	Campath®	Hm	CD52	B-CLL	B-CLL[d]	A, P, F	10.4[e]	$108.0	0.21
certolizumab pegol	Cimzia®	Hm	TNF	CD		P	n/a	n/a	n/a
gemtuzumab ozogamicin	Mylotarg®	Hm	CD33	AML		P, A, O	6.5	$60.0	0.12
muromonab-CD3	Orthoclone Okt3®	Mu	CD3	OR	OR		n/a	$150.0	0.30
efalizumab	Raptçiva®	Hm	CD11a	PS			10[e]	$163.0	0.32
abciximab	ReoPro®	Ch	GP IIb/IIIa	AC	CI	O	n/a	$380.0	0.75
basiliximab	Simulect®	Ch	CD25	OR		O, P	n/a	$300.0	0.59
eculizumab	Soliris®	Hm	C5	PNH		O, P	n/a	$230.0	0.45
natalizumab	Tysabri®	Hm	a-4 integrin	MS	CD	A	10.6[e]	$100.0	0.20
panitumumab	Vectibix®	Hu	EGFR	mCRC		A, P, F	7.4	$365.0	0.72
omalizumab	Xolair®	Hm	IgE	AA			9.7	$472.0	0.93
daclizumab	Zenapax®	Hm	CD25	OR	OR[p]	O, P	n/a	$60.0	0.12
ibritumomab tiuxetan	Zevalin®	Mu	CD20	NHL		P, A, O, F	10.2	$17.0	0.03

Abbreviations: Structure: Ch, chimeric; Hm, humanized; Hu, human; Mu, murine. Regulatory Path: A, accelerated approval; F, fast-track; P, priority review; O, orphan indication. 1-, first-line therapy; a, conditional approval; b, rituximab refractory; c, refractory to chemotherapy; d, single-agent; e, estimate; m, metastatic; n/a, information not available; p, prophylaxis. Sources: 20 Compounds that defined biotech, Signals online magazine at www.signalsmag.com; ReCap database; Biopharmaceutical Products in the U.S. and European markets 6th edition, Ronald A. Rader, ed; Pharma Sales and BioPharmInsights databases; Reichert JM, Ph. D.; personal communications. Development times and sales estimates for some Second Tier mAbs are based on limited information.

(ranibizumab) and prophylaxis of RSV viral infections in children (palivizumab). Of the fourteen Second Tier mAbs, five are for oncology indications (tositumumab, alemtuzumab, gemtuzumab ozogamicin, panitumumab and ibritumomab tiuxetan), three for autoimmune diseases (certolizumab pegol, efalizumab and natalizumab), and six for specialized indications (abciximab, basiliximab, daclizumab, eculizumab, muromonab and omalizumab). Oncology and autoimmune diseases are the most successful indications, with five mAbs having sales in excess of $3 B.

The data in Table 1 indicate that, in addition to high sales, First Tier mAbs share three other success factors: relatively short approval time, rapid label expansion and extensive use of FDA programs designed to accelerate drug approval such as Fast Track and Priority Review. The clinical development of First Tier mAbs has followed the typical biotechnology path, which consists of securing approval for an initial indication, referred to here as the "landing indication", followed by a process of label expansion to achieve maximum market penetration. For First Tier mAbs,

the average time lapse between Investigational New Drug (IND) filing and Biological License Application (BLA) for the landing indication approval was a remarkably short six years, compared to the almost eight years average for all mAbs approved.[2] The fastest total clinical and approval time was for palivizumab, with 3.6 years from IND to BLA approval, and the longest for cetuximab, with 9.7 years.

Short development phases correlate with a choice of landing indication that is in alignment with the therapeutic and pharmacological properties of the mAb. For example, the landing indication for rituximab was non-Hodgkin Lymphoma, for which this mAb showed highly promising clinical activity even in the phase I trial. Together with well-designed and executed clinical trials, this led to approval in slightly less than five years under Orphan Drug and Priority Review programs. With the exception of infliximab, which failed on acute sepsis as the initial landing indication, all First Tier mAbs were successful on the first indication chosen. Even in the case of infliximab, by changing focus from sepsis to Crohn Disease (CD) as landing indication, Centocor, the sponsor company, was able to secure approval in only 4.6 years.

Cetuximab represents an example of the delay in development that can result from suboptimal execution of clinical trials. After the FDA rejected the first clinical data submitted,[3] ImClone, the sponsor company, was able to rely on the trials conducted by partner Merck KGaA to secure approval under Fast Track and Priority Review. However, the delay contributed to a total development and approval phase of 9.7 years for the product.

Regulatory approval of the Second Tier mAbs certolizumab pegol and panitumumab is too recent to determine their ultimate position in the marketplace, and they both have the potential to become First Tier mAbs by capturing sales from established products. Certolizumab pegol, approved in April 2008, targets TNF and panitumumab, approved in September 2006, targets EGFR.

Tositumomab and ibritumomab tiuxetan are two Second Tier mAbs that have the same molecular target as the First Tier mAb rituximab. These mAbs are conjugated to radioisotopes, and thus their mode of action combines both the therapeutic effects of the anti-CD20 mAb with the targeted delivery of the radioisotope. In spite of the excellent clinical performance of both products, fewer than 10% of eligible patients receive these drugs. One possible reason cited is that most oncologists are not licensed to administer radioactive drugs and are reluctant to cede control of the patient to a nuclear-medicine specialist. There is also a perception that tositumomab should be used only after chemotherapy failure, whereas data indicate that use immediately on relapse from rituximab is best.[4] In fact, based on clinical data, one could argue that tositumomab could lead to longer remissions than rituximab if used as first-line NHL therapy. The history of these two mAbs shows how perceptions, the requirement for unusual handling of a drug and the reluctance of doctors to refer patients can result in barriers to successful commercialization, even if the mAb is clinically effective. The complexities involved in handling these radioactive compounds also resulted in development times in excess of a decade for each product.

Four Second Tier mAbs (omalizumab, eculizumab, basiliximab and abciximab) target niche indications and have annual sales of more than $200 M. For example, the orphan drug eculizumab targets PNH, a rare disease with only 8–10,000 patients in Europe and North America, and basiliximab targets organ rejection in renal transplantation. The ultimate profitability of these mAbs will depend on the success of current efforts to expand their labels and global markets. Sales of natalizumab, once considered a candidate for First Tier mAb, continue to be limited by the occurrence of progressive multifocal leukoencephalopathy in some patients (PML).[5]

mAb Engineering

Advances in mAb engineering are driving a transformation of the field, resulting in new drugs with decreased immunogenicity and improved potency, specificity and stability. The impact is already evident by the replacement of murine and chimeric mAbs by fully human mAbs such as adalimumab and the successful development of products such as ranibizumab and certolizumab pegol. The human mAb adalimumab, created using the Cambridge Antibody Technology phage display technology, has become a First Tier mAb in spite of entering the market after the competing products infliximab and etanercept had become top-selling drugs. Certolizumab pegol, a Fab fragment engineered for increased half-life and less frequent dosing by conjugation to polyethylene glycol (PEG), is now competing against the older anti-TNF drugs, including adalimumab. Ranibizumab, an engineered antibody fragment derived from bevacizumab, targets "wet" age-related macular degeneration (AMD) and has become the standard of care for the indication. The introduction of newly engineered mAbs that will compete with the currently commercialized drugs and expand the range of clinical indications is expected to continue as a trend,[6] subject to the considerations on reimbursement and pricing discussed below.

Biosimilar mAbs

Copies of off-patent biological therapies are commonly referred to as "biosimilars" to denote that the structural and manufacturing process identity of small-molecule generic drugs may not be achievable with proteins. The complexities of the molecules and the lack of a regulatory framework for approval in the U.S. makes it unlikely that biotechnology companies are dedicating a significant effort to biosimilar mAbs. However, driven by the high cost of these drugs, the interest in biosimilar mAbs remains high. Schneider and Kalinke have analyzed the possible regulatory path for mAb biosimilars in Europe.[7] The authors' main conclusions are that the current EMEA guidelines are only partially suitable for potential mAb biosimilars and that approval would entail case-by-case discussions between sponsors and regulatory agencies regarding the generation of analytical chemistry, chemistry, manufacturing and control (CMC), non-clinical and comparative clinical trials data.

As an example of the interest in biosimilar mAbs, India's Dr. Reddy's has launched Reditux®, an anti-CD20 mAb that the company claims is the first biosimilar mAb. Although approved in India, it seems unlikely that Reditux® would have sufficient data to comply with the strict safety, efficacy and manufacturing

controls standards of developed countries. One could argue that if Reditux® establishes a good track record in India over a period of several years, it would be tempting for Western nations to provide a regulatory path for the drug if the price differential is significant. However, Dr. Reddy's has priced Reditux® at about half the cost of Rituximab®,[8] far from the price differential of small-molecule generic drugs, which can cost as little as one-tenth of the original drug. It is likely that, if a regulatory path is provided in developed countries, the cost of bringing Reditux® into compliance would have to be built into the price of the drug, thus closing even further the price gap between the original mAb product and its presumed copy.

Research by our group that included interviews with both European and US regulatory experts suggests that approval of biosimilar mAbs would not differ substantially in time and cost from the approval of improved mAbs against the same molecular target. Additionally, mAbs eligible to become biosimilars are older murine or chimeric versions that will likely be replaced by human or humanized mAbs. Taken together, these points suggest that the main competition to commercialized mAbs will continue to arise from newly engineered mAbs rather than by biosimilars.

The absence of generic threats makes mAb drugs more attractive to biotechnology companies than small molecule drugs, which face aggressive generic competition upon the expiration of patents ("patent cliff"). Although mAbs are vulnerable to competition from new generations of engineered mAbs, this process is not as abrupt as the "patent cliff." However, this same property of mAbs is of great concern to health care payers, who currently face open-ended high costs.

Reimbursement

The level of sales achieved by First Tier mAbs indicates the willingness of healthcare payers to reimburse for the cost of the drugs. Although mAb drugs have always been costly, when there were only a few on the market the impact on overall health care expenses was limited. However, by the end of 2008 specialty pharmaceuticals, a category that includes mAbs, will account for 26% of all US drug costs.[9] In the particular case of mAbs, the large number of new drugs under development, the sales growth of the First Tier products, and the absence of generic competition introduces dynamic tension within the global health care systems. The most pronounced effects are occurring in the US where both public and private payers are responding to the skyrocketing costs of specialty pharmaceuticals by adopting short-term, or stopgap, steps and by supporting long-term measures that would profoundly transform the way mAbs are developed and commercialized. One of the stopgap tools used to control costs is co-insurance or Tier 4 payments, which require patients to share a percentage of drug costs rather than paying fixed co-pays.[10] With some health plans requiring more than 30% cost sharing and some mAb therapies costing upwards of $100,000, the financial burden on patients can be significant. Other tools employed by payers are prior authorizations, formulary management and step therapies.[9]

Although the more restrictive reimbursement practices are not yet reflected in the sales listed in Table 1, some situations with approved mAbs are a harbinger of the environment new products will encounter. First, in those cases where a new product is an improved version of an existing mAb, or it competes against an established therapy, payers expect comparative clinical data from sponsors. For example, soon after approval of ranibizumab, ophthalmologists discovered that the parent drug bevacizumab, which is cheaper and more widely available, appears to offer similar efficacy.[11] For a 20% co-pay in an insurance plan, ranibizumab would cost $400 versus $150 for bevacizumab. A cost-effectiveness model concluded that, to justify the higher cost of ranibizumab, bevacizumab would have to be only 40% as effective as the improved version.[11] Sponsor Genentech did not conduct head-to-head trials with the two drugs, and then took some controversial measures to restrict the off-label use of bevacizumab for AMD, such as restricting sales to compounding pharmacies, which provide aseptic re-packaging into the smaller doses required for ophthalmology use.

The NIH National Eye Institute has started a multi-center comparative clinical trial of bevacizumab versus ranibizumab, with results expected in 2010 (CATT, Comparison of AMD Treatments Trials). The outcome of this trial may affect reimbursement for bevacizumab. Pending legislation for the creation of the Health Care Comparative Effectiveness Research Institute (Senate Bill S.3408), which would conduct comparative trials on behalf of payers, suggests that the trend started with the CATT trial may be expanded in the future.

The second trend related to reimbursement affects primarily mAbs for solid tumor indications, and reflects a divergence of opinion between oncologists, the FDA and payers. This is illustrated by the provisional approval of bevacizumab for first line treatment of HER-2 negative metastatic breast cancer on the basis of progression-free survival (PFS) as a surrogate endpoint for overall survival (OS), in spite of only a marginal improvement in PFS, no improvement in OS, and significant toxicity.[12]

Whereas some payers claim that the benefit of the drug does not justify the cost, many oncologists and the FDA's Office of Oncology Products support the use of the surrogate endpoint as necessary in a field where the use of multiple therapies can obscure the impact of a single drug on survival.[12] At least for now it is likely that the use of PFS as an endpoint will continue, but companies pursuing a development path based on the use of this surrogate endpoint may encounter barriers to reimbursement of their drugs until their clinical effectiveness in combination therapies is clearly demonstrated.

Conclusions and Discussion

Our review of development and marketing data for mAbs reveals several major trends. At the science level, the most significant positive trend is the evolution of mAb engineering which is resulting in new mAbs with enhanced effector functions, improved half-life, tumor penetration, and stability, and lower production costs.[6,13-15] At the business level, the lack of generic competition makes mAb drugs more attractive than their small-molecule counterparts, but a significant negative trend exists due to changing reimbursement policies aimed at controlling the spiraling costs of specialty pharmaceutical drugs.

Improvements in mAb engineering have already been incorporated in commercialized mAbs and, with more than 50 IND applications submitted in 2007 for mAb products,[16] it is likely that many engineering concepts will be tested in the clinic in the coming years. Whereas some of these new mAbs are directed towards known molecular targets, others seek to extend the range of therapeutic indications beyond the traditional oncology and autoimmune fields. Products under development also include combinations of mAbs ranging from two to 15–20, with the latter designed to replace polyclonal antisera. Depending on the outcome, and on how effective companies are at managing their products in a challenging environment, new entrants may significantly change the list of First Tier mAbs, segmenting the market for current mAbs and adding new therapeutic indications.

In oncology, which is arguably the most important indication for mAbs,[17] these drugs have shown significantly more success in hematological malignancies that in solid tumors. This may be due in part to the limited solid-tumor penetration of large macromolecules. The manipulation of molecular size, charge, valence and binding affinity through mAb engineering may improve the effectiveness of mAbs in solid tumors.[18] Potency is another crucial area for mAb engineering, with a potential impact on all indications. In the particular case of oncology, increases in potency could allow the use of mAbs without concomitant use of chemotherapy drugs. After all, the original premise of targeted drugs was to avoid the use of indiscriminately cytotoxic drugs. Two exciting areas for mAb engineering are the engagement of the T-cell system through the use of bifunctional[19] and trifunctional mAbs[20] and the design of immunoconjugates with better therapeutic ratios than current drugs.[21]

Reimbursement and mAb engineering are closely tied concepts because, in the end, drugs that can show cost-effective clinical efficacy are reimbursed by payers. The stopgap measures to control cost that US payers currently use are intrinsically flawed because they target cost regardless of effectiveness. The long-term trend is to replace these measures with reimbursements made on the basis of evidence-based clinical data or outcome-based models, by which companies are reimbursed only for patients that show an objective response. Our discussions with payers reveal a perception that clinical trials used for drug approval generally fail to provide the information necessary to make sound reimbursement decisions, a situation that is part of a larger "clinical gap" problem[22] and includes the limited disclosure of clinical data.[23] An option that is gaining momentum is the mandatory publication of registered trials. Payers support evidence-based treatment guidelines such as those developed for oncology by the National Comprehensive Cancer Network (NCCN), and are willing to finance an official comparative clinical trials initiative. It is clear that companies developing new mAb products have to plan for greater transparency in their clinical development, including head-to-head comparisons with existing drugs and timely publication of results.

Another important change is the decline of the "buy and bill" business model, particularly relevant to oncology practices. Under this system doctors buy drugs and submit insurance claims after treatment. Declines in reimbursement and more frequent denials of claims are forcing private oncology practices to either drop the model or limit it to those drugs with the highest margins. This is seen by payers as a bias in favor of expensive drugs, and thus a target for control.[9] Furthermore, patients increasingly demand access to experimental drugs through clinical trials that may not be offered at private practices. Thus, the future appears to favor cancer centers and community hospitals over independent oncology practices, a trend that biotechnology companies developing mAbs have to take into consideration.

Given that for all indications covered by mAbs there are segments of the patient base that fail to respond or that become resistant to therapy, the most rational cost-saving measure is to develop tools for predicting response. In addition to the *HER2/neu* overexpression test for trastuzumab and the *EGFR* expression tests for cetuximab and panitumumab,[12,24] K-ras status has shown to have predictive value for bevacizumab in mCRC patients.[25] As molecular and imaging tools become validated as to their value in segmenting patient populations on the basis of likelihood of response to treatment, the market for individual mAbs will become smaller but more effectively focused on positive outcomes. In the meantime, outcomes-based reimbursement is an imperfect but immediately available approach to tie cost of care to efficacy.

On the basis of the observations made in the course of our consulting practice, which are generally in good alignment with the experience of other consulting firms,[26] our current discussions with portfolio companies developing new mAbs center on the following areas:

Careful targeting of landing indication. Always important, the choice of landing indication is now even more so because one of the possible consequences of a more restrictive reimbursement environment may be slower label expansion, and thus longer reliance on the revenue from the landing indication. An increased use of biomarkers may result in more diagnostic tools being used to define landing indications.

Risk mitigation in comparative trials. Biotechnology companies are often reluctant to conduct head-to-head trials with established drugs because of the risks involved, and the perception that regulatory approval will continue to be sufficient to succeed in the marketplace. We believe that comparative trials may become unavoidable, particularly for new mAbs seeking to capture a niche currently occupied by an established drug. The risks involved, which may be compounded by the possible mandatory disclosure of clinical trial results, have to be managed during the development program.

Market research and pricing. Old market research methodologies have lost much of their relevance, primarily because of the increased influence of payers on treatment decisions, which often happens at the expense of the autonomy of doctors. In fact, some of the most important discussions we have had recently have been with specialty pharmacists familiar with mAbs and that, directly or indirectly, work for payers. Consistent with a correction of the industry's overreliance on marketing, pricing should no longer be a decision made by marketing people at the pre-launch stage, but should be an interdisciplinary effort that begins at very early stages of product development

Early integration with diagnostic biomarkers. Most therapeutic indications for mAbs are only broad labels for heterogeneous patient populations. Thus, the current expectation for new drugs is that they will be integrated with biomarker tools to help identify those patients most likely to respond to treatment. We have seen strong support from payers for the use of biomarkers in treatment decisions.

In summary, our analysis indicates that the commercial success of First Tier mAbs derives from a process that starts with the choice of landing indication for an unmet clinical need, and progresses through rapid regulatory approval based on clear clinical data, subsequent label extension to maximize market penetration, and favorable reimbursement decisions from payers. As the maturation of the field brings forth both an unprecedented number of new drugs under development and a concomitant increase in economic challenges, achieving commercial success with new mAb products will require sponsoring companies to show significant creativity and ability to adapt to challenging circumstances.

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