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Research paper

# The therapeutic antibodies market to 2008

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**Abstract**

The therapeutic biologics market is currently dominated by recombinant protein products. However, many of these products are mature, and growth of the biologics market will increasingly rely on the expansion of the therapeutic monoclonal antibody sector. Successive technology waves have driven the growth of the monoclonal antibody sector, which is currently dominated by chimeric antibodies. Chimeric products, led by Remicade and Rituxan, will continue to drive market share through to 2008. However, over the forecast period, humanized and fully human monoclonal antibodies, together with technologies such as Fabs and conjugated antibodies, will play an increasingly important role, driving monoclonal antibody market growth at a forecast compound annual growth rate of 20.9%, to reach $16.7 billion by 2008. In terms of therapeutic focus, the monoclonal antibody market is heavily focused on oncology and arthritis, immune and inflammatory disorders, and products within these therapeutic areas are set to continue to be the key growth drivers over the forecast period. Underlying the growth of the market is the evolution of the monoclonal antibody company business model, set to transition towards the highly successful innovator model.


*Keywords:* Monoclonal antibody; Chimeric; Murine; Humanized; Fabs; Fully human; Market analysis

## 1. Introduction

In the early 1970s, the biotechnology industry began to benefit more directly from an explosion in public funding. From the middle 1970s onwards, substantial advances in physiology, pharmacology, enzymology and cell biology, with the vast majority stemming from publicly funded research, led to enormous progress in the ability to understand the biochemical and molecular roots of many diseases. This new knowledge had a profound impact on the process of discovery for new drugs. Advances in molecular genetics and recombinant protein (rDNA) technology opened an entirely new frontier for biopharmaceutical innovation.

The application of these advances initially followed two relatively distinct technical trajectories. The first used advances in genetics and molecular biology as tools to enhance the productivity of the discovery of conventional 'small molecule' synthetic chemical drugs. Meanwhile, the second trajectory was rooted in the use of molecular biology as a process technology to manufacture protein-based biomolecules.

The production of murine monoclonal antibodies (mAbs) was first reported in 1975 [1] and, by 1980, mAbs had entered studies in humans. Chimeric and humanized mAbs, first reported in 1984 [2] and 1986 [3], respectively, were developed to address the problems associated with the murine mAbs. Such problems included their short serum half-life and the human antimouse antibody (HAMA) immunogenic response [4]. Early antibody specialists initially advanced their basic technological platform in the 1980s helped mainly by public and venture capital funding.

Later, as technology evolved further, the sector was able to attract a wave of alliance networking with the large pharma sector, allowing several companies in the 1990s to build their own or partnered pipelines. Eventually, some were able to create in-house manufacturing and sales and marketing capabilities to integrate their businesses further,

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Table 1
The current leading monoclonal antibodies approved to date, highlighting sponsor company, the mAb indication, type and stage of development, the date of approval and the sponsor company website

| Brand name | Common/chemical name | Sponsor company | Therapy area | Stage | US approval | Website address |
|---|---|---|---|---|---|---|
| *Murine* | | | | | | |
| Orthoclone OKT3 | Muromonab-CD3 | J&J | AIID | M | Jun-1986 | www.jnj.com |
| Panorex | Edrecolomab | Glaxo/Centocor | ONCO | D | n/a | www.gsk.com/ www.centocor.com |
| *Chimeric* | | | | | | |
| ReoPro | Abciximab | Centocor | CV | M | Dec-1994 | www.centocor.com |
| Rituxan | Rituximab | Biogen-IDEC | ONCO | M | Nov-1997 | www.biogen.com |
| Simulect | Basiliximab | Novartis | AIID | M | May-1998 | www.novartis.com |
| Remicade | Infliximab | Centocor | AIID | M | Aug-1998 | www.centocor.com |
| Erbitux | Cetuximab | ImClone Systems | ONCO | M | Feb-2004 | www.imclone.com |
| *Humanized* | | | | | | |
| Zenapax | Daclizumab | Protein Design Labs | AIID | M | Dec-1997 | www.pdl.com |
| Synagis | Palivizumab | MedImmune | ID | M | Jun-1998 | www.medimmune.com |
| Herceptin | Trastuzumab | Genentech | ONCO | M | Sep-1998 | www.gene.com |
| Campath | Alemtuzumab | Millennium/ ILEX* | ONCO | M | May-2001 | www.mlnm.com/ www.ilexonc.com |
| Raptiva | Efalizumab | Genentech | AIID | M | Oct-2003 | www.gene.com |
| Xolair | Omalizumab | Genentech | RESP | M | Jun-2003 | www.gene.com |
| Avastin | Bevacizumab | Genentech | ONCO | M | Feb-2004 | www.gene.com |
| *Conjugated* | | | | | | |
| Mylotarg | Gemtuzumab ozogamicin | Wyeth | ONCO | M | May-2000 | www.wyeth.com |
| Zevalin | Ibritumomab tiuxetan | Biogen-IDEC | ONCO | M | Feb-2002 | www.biogen.com |
| Bexxar | Tositumomab-I131 | Corixa | ONCO | M | Jun-2003 | www.corixa.com |
| *Human* | | | | | | |
| Humira | Adalimumab | Abbott | AIID | M | Dec-2002 | www.abbott.com |

AIID, arthritis, inflammation and immune disorders; CV, cardiovascular; ID, infectious disease; ONCO, oncology; RESP, respiratory; D, discontinued; M, currently in the market; *, ILEX is now part of genzyme; Source: datamonitor, company-reported information.

towards the fully integrated pharma or biotech company model.

Driving this business activity was the market's need to generate an economic environment of sustainable profitability. The attractiveness of antibody developers to investors is closely linked to the successes or failures in other biotech technological platforms such rDNA or gene therapies. During the late 1990s the perception that genomics would rapidly revolutionize medical practice had created a bull market with cross-platform unrealistic stock overvaluations, driving up the market capitalization of public mAb developers.

Later, as investors realized that the use of genomics data could take more than 10 years to create real drug pipelines, the industry entered a bearish environment with significant stock devaluations and a very low level of IPO (Initial Public Offering) activity, even in areas, where biotech activity (e.g. antibody development) was maturing and concentrating on actual drug development rather than data exploration.

The exit strategy from the current bear market revolves around the creation of sustainable profitability.

Utilizing a number of verified industry databases [5] and in-house primary and secondary analysis to analyse the antibody market, Datamonitor [6] has constructed a database that includes the pipelines, technologies and partnerships of 95 key companies and a 'virtual' dialogue with some of the antibody sector's industrial leaders to produce thorough analysis of the sector's growth potential. Of these 95 companies, the leading companies and their products are detailed in Table 1.

## 2. Methods

In analyzing the antibody market, Datamonitor has constructed a database of 376 preclinical-to-market products that includes the pipelines, technologies and partnerships of 95 key companies (Fig. 1). This analysis was performed in May 2004. Table 1 highlights the characteristics of the leading marketed mAb therapeutics.

Analysis was performed on this information, utilizing a bottom-up methodology as shown in Fig. 1, to draw out the strategy underlying mAb market dynamics. The database formed the basis to identify and benchmark the leading biotech and pharma antibody-oriented business models according to strategic, portfolio and financial measures, enabling Datamonitor to evaluate the most successful operating strategies.

The analysis assesses the strategic implications for the antibody companies as well as the most significant steps that the industry's emerging players and leaders are taking to

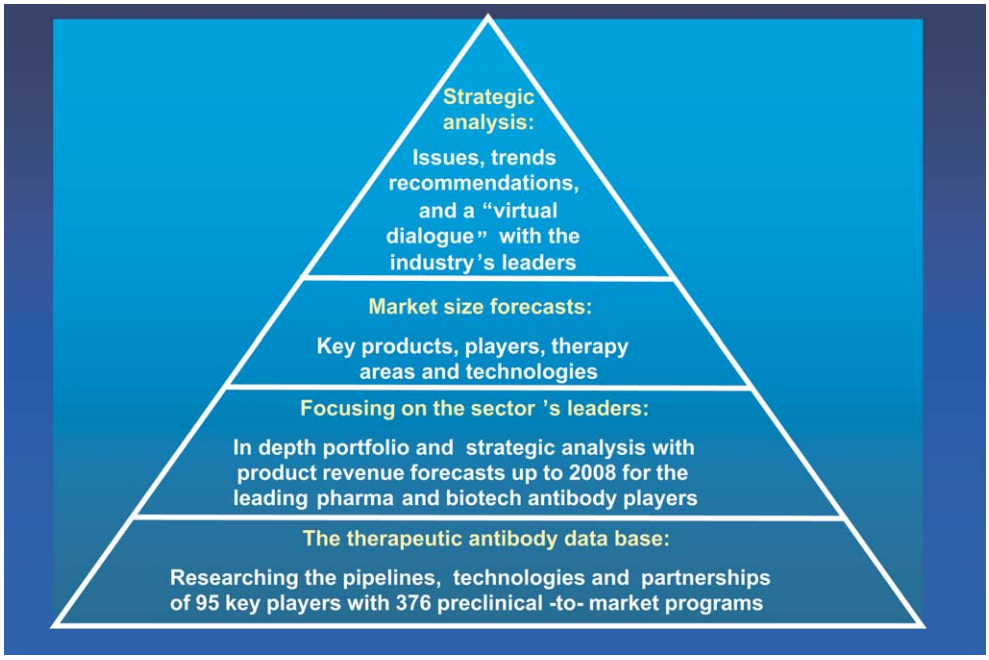


Fig. 1. The structure of Datamonitor's analysis methodology of the therapeutic antibody market.

increase the degree of innovation in their businesses, integrate their supply chain and improve their strategic position in the market. This information was then used to build total market size forecasts and identify issues and trends affecting the industry over the forecast period.

### 2.1. Segmentation of technology platforms

Table 1 highlights the key marketed antibodies and antibody developers. These antibodies have been split into key groups, which are discussed briefly below.

### 2.2. Murine

Murine antibodies are 100% murine protein and for this reason, therapeutic applications of murine mAbs have been limited by their side-effect profile, their short serum half-life and their inability to trigger human immune effector functions, which reduce the efficacy of the mouse antibody as a therapeutic [4]. At the heart of these effects is the allergic-like HAMA response [7]. This is, where a mouse antibody is detected by the human immune system as an antigen and the human immune system generates its own human antibodies against the introduced mouse antibody.

### 2.3. Chimeric

Chimeric antibodies consist of components of both mouse and human antibodies, constructed using genetic engineering. The mouse protein component is taken from the variable region (Fv) of the mouse antibody, which contains the antigen-binding region. Murine protein in a chimeric antibody typically accounts for 33% of the total protein, while the remaining 67% of the antibody, originally comprising of the mouse constant (Fc) domains, have been replaced by human constant domains. Chimeric antibodies are designed to minimize the HAMA antigenic response triggered by the antigenic part of the mouse component, while retaining a high specificity. However, although the immunogenicity profile is reduced, chimeric antibodies such as Centocor/JNJ's Remicade (infliximab) can still trigger a HACA response (Human Anti-Chimeric Antibodies) [8]. This is similar to the HAMA response and reduces the antibody's efficacy.

### 2.4. Humanized

Within the variable region of the antibody, there are hypervariable regions that construct the antigen binding site [9]. To counteract both the HAMA and HACA responses associated with murine and chimeric antibodies, the hypervariable regions from a mouse antibody are inserted into a human antibody using genetic engineering to create humanized antibodies [10]. Murine regions account for 5–10% of the humanized antibody, which reduces the immunogenic profile of the antibody, and clinical trial data has shown that these antibodies are associated with minimal or no immunogenic responses.

### 2.5. Fully human

To reduce the risk of immunogenicity further, antibodies have been developed that contain 100% human proteins. Fully human antibodies can be obtained from human cells or

genetically engineered mice [11]. In addition to a lower side-effect profile, there is potential to use a lower dose size and frequency of dosing use of fully human antibodies, since they are likely to be eliminated less rapidly.

### 2.6. Conjugated

In addition to developing more specific and less immunogenic antibodies, research has also been carried out into enhancing the efficacy of action by conjugating them with a payload of chemotherapeutic drugs or radioactive isotopes [12]. This combines the specificity of the antibody to optimize target specificity with the therapeutic efficacy of the conjugated product, since the concentration of the payload therapeutic is very high at the tumor site, without the dose-related side-effects associated with systemic administration [13].

### 2.7. Fragment

Antibody fragments are known as Fabs and consist of one antigen-binding arm of the antibody. Fragments lack the Fc portion, which serves to bind various effector molecules of the immune system, and they have key advantages over complete antibodies. Compared to complete antibodies, Fab fragments can be produced using microbial expression systems [14], which significantly reduces the cost of production, and they are better at penetrating solid tumors [15]. However, it has been observed that the activity of some mAbs has been reduced without the Fc region, which may reduce the efficacy of Fab fragments in certain scenarios [16].

### 2.8. Forecasting methodology

The forecast revenues of each therapy area are based on forecasts of individual products within each therapy area. Individual forecasts are made for the key marketed products, including the largest products within the therapy area and any newly launched products with high growth potential. In addition, revenues from any products under clinical development that are likely to be launched before 2008 within each therapy area are also individually forecast.

To forecast individual products, specific growth curves are fitted to historical sales figures. As exemplified in the test scenario in Fig. 2, where appropriate, the baseline forecast is then modified with specific events (in this case, competition from a next-generation competitor with higher efficacy and lower side-effect profile) to produce a final sales forecast for the individual product. The size of the modification depends on the impact that each event is forecast to have on the drug's overall annual revenues. To validate these forecasts, forecasts from previous years are reviewed and compared against actual revenues. To forecast products currently under clinical development, first-year sales are predicted by identifying a series of attributes that will contribute to the initial market share and the product is then scored on each of these attributes. An example of such an attribute would be whether the drug was the first to the market of a particular class. The first-year sales are then fitted to a growth curve reflective of product class and modified, where appropriate.

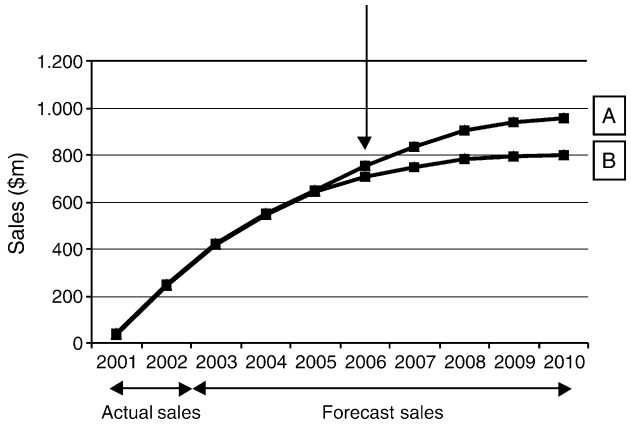


Fig. 2. Example of Datamonitor's drug forecasting. (A) indicates the unevented baseline forecast—in other words, the forecast sales trajectory with no modifications; (B) indicates the baseline impacted by a negative event in 2006 (indicated by the arrow), leading to a lower forecast sales trajectory than the unevented baseline forecast. An example of such a negative event may be the launch of a competitor product with greater efficacy or a lower side-effect profile.

## 3. Results and discussion

### 3.1. Key technological trajectories

Between 2001 and 2002, the value of the therapeutic antibody market grew by 37.5% to $5.4 billion, of which chimeric antibodies generated 70%. However, as Fig. 3 highlights, the technological focus of the antibody sector is changing as humanized and fully human products dominate the pipeline. Of the 376 development programs identified by Datamonitor (from preclinical to marketed) across 95 key companies, 132 are currently in clinical development, of which 92 involve humanized (55 or 41.7% of the antibody clinical pipeline) and fully human products (37 or 28% of the clinical antibody pipeline). The strength of humanized and human platforms is reflected in the product approval trajectories in terms of technological exposure between 2003–2008, as highlighted in Fig. 4. Additionally, new technologies, including conjugated antibodies and Fabs, are expected to rise in importance, accounting for 26 programs (20 conjugated and 6 Fabs) or 19.7% of the antibody clinical pipeline.

Datamonitor's analysis suggests that there will be two major approval waves over the next four years. More specifically, the period 2004–2008 will see the launch of eight fully human antibodies, of which six are projected to

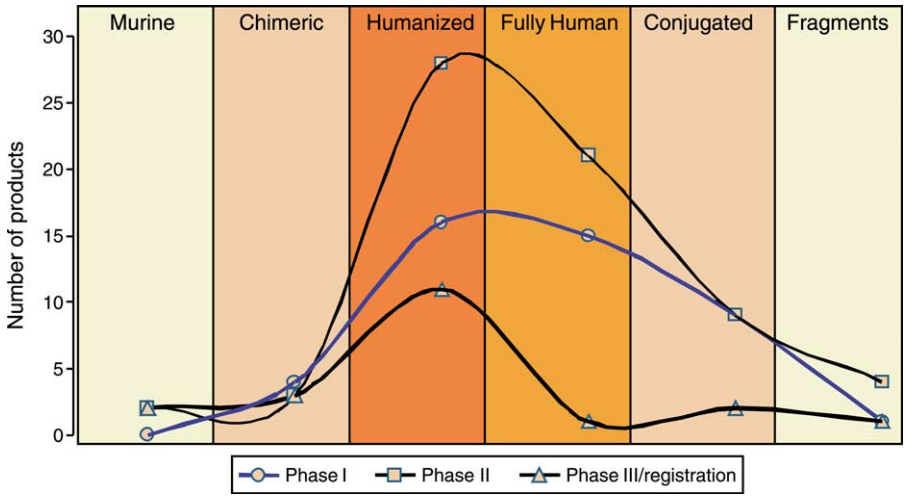


Fig. 3. Technological exposure of the antibody clinical pipeline, 2004.

receive approval between 2007 and 2008. In addition, there will be six launched humanized products of which three are set to receive approval in 2005. Additionally, four marketed conjugated antibodies are forecast to be launched in 2004, 2006 and 2008, together with one fragmented antibody set for launch in 2006. Based on these trends, the global therapeutic antibody market is forecast to grow at a compound annual growth rate (CAGR) of 20.9% reaching $16.7 billion in 2008. Current marketed products are expected to continue to dominate the market over the forecast period, with chimeric antibodies led by Remicade and Rituxan representing 49.3% of sales. The second most important technology in terms of 2008 sales will be humanized antibodies with sales forecast to grow from $1.4 billion to $5.2 billion, capturing a 31.2% market share by 2008. In addition, fully human antibodies are expected to reach 2008 sales of $1.9 billion representing 11.4% of the market share in 2008.

### 3.2. Key therapeutic areas

Monoclonal antibodies are set to play a significant role in the treatment of a wide number of indications, including oncology, asthma, autoimmune diseases, poisoning, viral infections and other diseases [17]. However, the antibody industry is heavily focused on oncology and arthritis, immune and inflammatory disorders (AIID), and as Fig. 5 illustrates, this focus is set to continue. In terms of the global antibody portfolio (from preclinical to marketed products), Datamonitor has identified 193 oncology programs, using

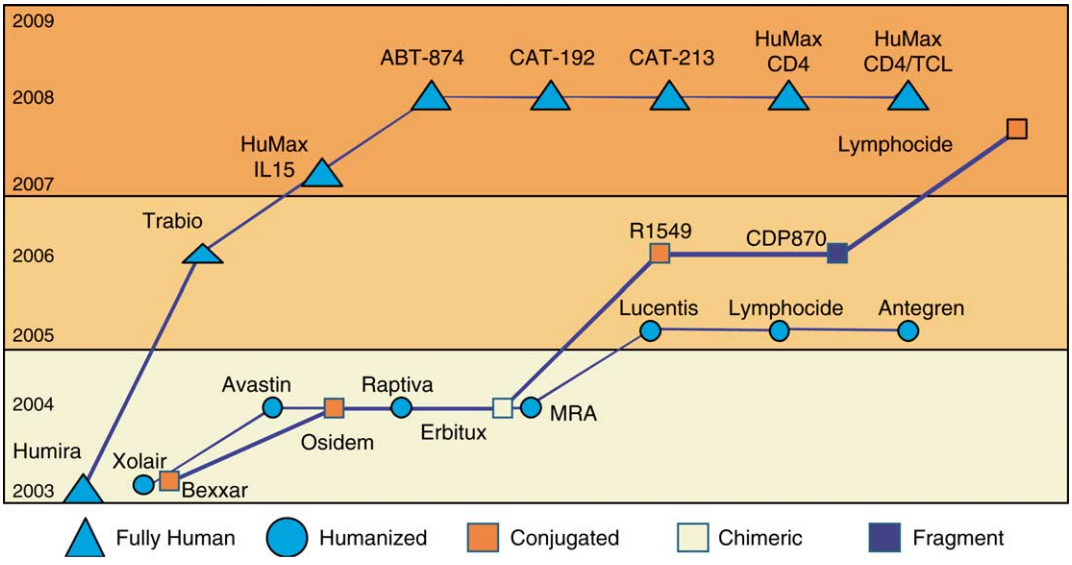


Fig. 4. New product approval trajectories in terms of technological exposure. *Antisoma/Roche's R1549 preliminary failure in Phase III could delay if not halt its approval.

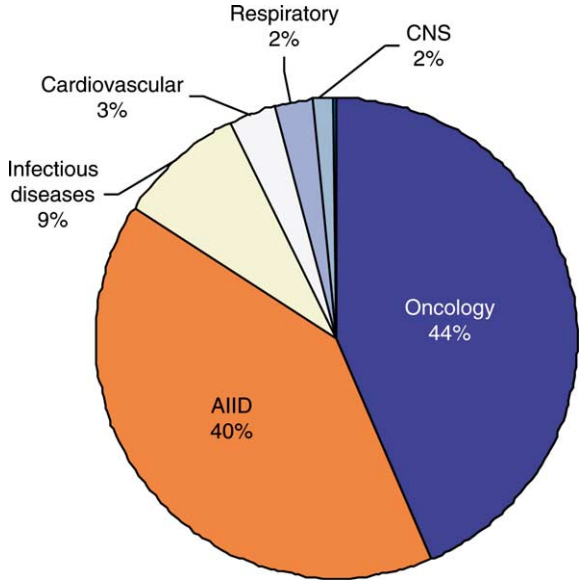


Fig. 5. Breakdown of antibody sales by therapy area, 2008. AAID: arthritis, inflammation and immune disorders.

in-house primary and secondary research, together with a number of verified industry databases [5]. These programs represent 51.3% of the antibody portfolio, followed by 81 AIID programs with a portfolio share of 21.5%. Together, these areas represent more than 72% of the global antibody portfolio. For the period 2004–2008, oncology will be the leading ethical income earner, with sales growing to $7.2 billion, representing a 44% market share. Meanwhile, AIID is expected to post stronger growth than oncology, as sales will double from $3 billion in 2004 to $6.7 billion in 2008, accounting for 40% of the global market.

### 3.3. Leading products

In Datamonitor's view, the sector's dependence on blockbusters will increase, with five antibody drugs forecast to achieve annual sales of over $1 billion by 2008 (Fig. 6).

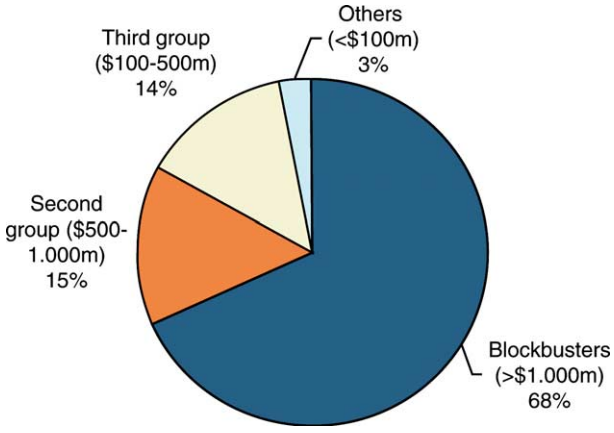


Fig. 6. Contribution of blockbuster antibodies to the sector's total ethical revenues, 2008.

These products (Rituxan, Remicade, Humira, Synagis and Herceptin) are expected to generate combined sales of over $11.4 billion in 2008, capturing a 68% share of the total monoclonal antibody market. The industry's leading antibody will continue to be J&J/Centocor's chimeric monoclonal antibody Remicade (infliximab), with sales forecast to reach $3.8 billion by 2008, representing almost one quarter of the market value.

Each of the five leading antibody drugs in 2003 is marketed by two or more companies to ensure maximum global penetration. The value of the therapeutic antibodies market makes it attractive to Big Pharma's sales and marketing engines. By 2008, Datamonitor forecasts that only two of the sixteen antibody-related therapies that will generate sales over $200m will be marketed without the involvement of a top 20 company. Both of these drugs will be marketed by Biogen-IDEC.

### 3.4. Business model evolution

The business model of the biotech antibody sector (Fig. 7) is evolving from technological provision and emerging drug development (early or late) to full integration. There are three routes to achieve this evolution: capturing venture capital funding, using R&D and/or licensing collaborations, and through merger and acquisition activity.

Many of the young, small companies currently developing or looking to out-license a basic technological platform are characterized by the need to differentiate new molecular structures that could compete with the current antibody technologies. The industry often remains sceptical to these attempts and waits for the first clinical results to decide upon licensing or acquisition activities. Typically, these young players will aggressively attempt to complete a number of preclinical studies before selecting a therapeutic target and entering the clinic. Until they reach a point, where their technology has some validation, the main preoccupation will be in attracting venture capitalists and private funding.

A number of emerging antibody players are currently combining in-licensing and in-house product development activities to further advance their clinical pipelines. For these companies, the key decision will be whether to grow their business through out-licensing, co-R&D and outsourcing or through independent organic development.

The major challenge and opportunity for the fully integrated antibody players will be to secure strong long-term revenue drivers. This process is expected to become more expensive as the biotech antibody leaders compete more with the leading pharma sector companies for products and novel technologies. Therefore, for some biotech players, consolidation may be essential to generate enough critical mass and become more competitive. A example of such consolidation is the recent merger of Biogen with

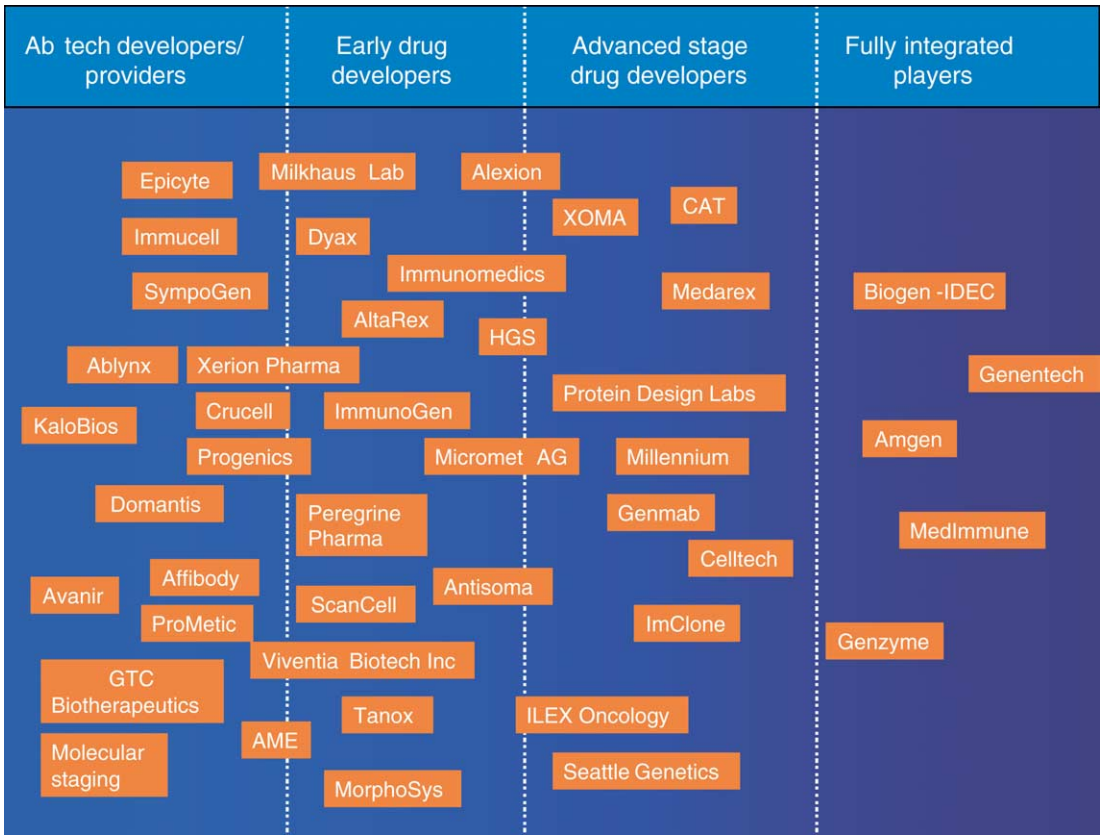


Fig. 7. The antibody sector's move from technology provision towards full integration.

IDEC to combine recombinant proteins and antibody technologies.

Overall, a company's competitive advantage will be decided to a considerable degree by the level of innovation it can achieve when operating in a environment of limited resources (for example private investments, licensing fees and milestones, manufacturing capabilities, technological and therapeutic complexities). Datamonitor has identified five key determinants that an antibody biotech player must optimize to become a highly competitive innovator. These include: (i) reducing development times of the product by accelerating the clinical trial testing, aided by developing novel and cost-efficient antibody development methods, (ii) building and maintaining well-protected intellectual property that covers, if possible, targets, products and development processes; (iii) increasing molecular evolution potential, by actively managing the lifecycle of the product, using processes such as reformulation, conjugation or pegylation, to aid market expansion; (iv) improving drug delivery systems for the product, and (v) building cost-efficient manufacturing capabilities.

## References

[1] G. Kohler, C. Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity, Nature 256 (1975) 495–497.

[2] S.L. Morrison, M.J. Johnson, L.A. Herzenberg, V.T. Oi, Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains, Proc. Natl Acad. Sci. 81 (1984) 6851–6855.

[3] P.T. Jones, P.H. Dear, J. Foote, M.S. Neuberger, G. Winter, Replacing the complementarity-determining regions in a human antibody with those from a mouse, Nature 321 (1986) 522–525.

[4] I. Aksentijevich, I.W. Flinn, Monoclonal antibody therapy with autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma, Cancer Control 9 (2002) 99–105.

[5] Industry databases used are: Investigational Drugs database, Thomson Current Drugs, 14 Great Queen Street, London WC2B 5DF, United Kingdom; BioSpace Clinical Competitive Intelligence System, Bio-Space, 300 Fifth Ave. South, Naples, FL 34102, USA; and IMS Lifecycle, IMS Health, 7 Harewood Avenue, London NW1 6JB, United Kingdom.

[6] Datamonitor plc, Charles House, 108-110 Finchley Road, London NW3 5JJ, United Kingdom.

[7] O.H. Brekke, I. Sandlie, Therapeutic antibodies for human diseases at the dawn of the twenty-first century, Nat. Rev. Drug Discov. 2 (2003) 52–62.

[8] S.B. Hanauer, Safety of infliximab in clinical trials, Aliment. Pharmacol. Ther. 13 (1999) 16–22.

[9] K. Rajagopalan, G. Pavlinkova, S. Levy, P.R. Pokkuluri, M. Schiffer, B.E. Haley, H. Kohler, Novel unconventional binding site in the variable region of immunoglobulins, Proc. Natl Acad. Sci. 93 (1996) 6019–6024.

[10] M.A. Holmes, T.N. Buss, J. Foote, Conformational correction mechanisms aiding antigen recognition by a humanized antibody, J. Exp. Med. 187 (1998) 479–485.

[11] M. Trikha, L. Yan, M.T. Nakada, Monoclonal antibodies as therapeutics in oncology, Curr. Opin. Biotechnol. 13 (2002) 609–614.

[12] T.A. Waldmann, Monoclonal antibodies in diagnosis and therapy, Science 252 (1991) 1657–1662.
[13] M. Harris, Monoclonal antibodies as therapeutic agents for cancer, Lancet Oncol. 5 (2004) 292–302.
[14] A.N. Weir, A. Nesbitt, A.P. Chapman, A.G. Popplewell, P. Antoniw, A.D. Lawson, Formatting antibody fragments to mediate specific therapeutic functions, Biochem. Soc. Trans. 30 (2002) 512–516.
[15] L. Sanz, B. Blanco, L. Alvarez-Vallina, Antibodies and gene therapy: teaching old 'magic bullets' new tricks, Trends Immunol. 25 (2004) 85–91.
[16] S.A. Eccles, Monoclonal antibodies targeting cancer: 'magic bullets' or just the trigger? Breast Cancer Res. 3 (2001) 86–90.
[17] M. Berger, V. Shankar, A. Vafai, Therapeutic applications of monoclonal antibodies, Am. J. Med. Sci. 324 (2002) 14–30.