Executive Summary

Since the award of a Nobel Prize for the technology that enabled the preparation of monoclonal antibodies in 1984, their utility has expanded far beyond their scientific use; they have become highly valuable therapeutic agents. Muromonab-CD3 (Orthoclone OKT3; Ortho Biotech) was the first of these to be approved for use in 1986, to prevent acute transplant rejection, and has been followed by an increasing number of other monoclonal antibodies, several of which were among the best-selling drugs in the world in 2010.

Progressive technological developments have led to the majority of antibodies now being developed evoking fewer non-specific immune responses, by steadily reducing the proportion of non-human DNA within the genes used to produce the antibodies. The use of humanized and, particularly, fully human antibodies addresses this issue, and methods to ensure retention of high affinity against the target antigen have been developed. Of the 34 monoclonal antibodies available for marketing during 2009 or 2010, 12 were humanized antibodies and eight were fully human antibodies, with five of the six antibodies approved in 2009 and 2010 fully human antibodies. And of these 34, five (murine) antibodies are approved as radiolabeled agents, with two cytotoxic conjugates and one antibody fragment also among the 34 approved antibodies. Two of these antibodies were recently withdrawn to add to three that had previously been withdrawn from marketing.

The commercial impact of monoclonal antibodies has been significant. By 2009, collective global sales of approved antibodies had reached $38 billion, with sales of the five leading antibody products alone generating revenues of $29.5 billion. Although one antibody was withdrawn from marketing in 2009 and one in 2010, three new antibodies were approved in each of those years.

Ten antibodies were approved for use in the treatment of various cancers by the end of 2010, with the withdrawal of MYLOTARG (gemtuzumab ozogamicin; Pfizer) offset by the approval of XGEVA (denosumab; Amgen) for the treatment of bone cancer. Aggregate sales of these products in 2009 were $19.1 billion, dominated by Roche's three blockbuster products Avastin (bevacizumab), Herceptin (trastuzumab), and RITUXAN (rituximab), with collective sales of $16.6 billion. Herceptin is used solely in the treatment of breast cancer, but the increasing usage of Avastin and RITUXAN to treat multiple conditions has led to their revenues each reaching nearly $6 billion in 2009. A further $2 billion of revenue was accounted for by the use of ERBITUX (cetuximab; ImClone) for the treatment of colorectal cancer and head and neck cancer.

Nine antibodies were available for the treatment of inflammatory and autoimmune diseases in 2009, although Raptiva (efalizumab; Genentech) was withdrawn during the year, with both ACTEMRA...
(tocilizumab; Genentech) and STELARA (ustekinumab; Centocor Ortho Biotech) approved in 2010. Four of these ten antibodies target the same antigen (TNFα), with each differing in the conditions for which they are currently approved; however, all are approved for the treatment of rheumatoid arthritis and one or more other inflammatory diseases. Sales of REMICADE (infliximab; Centocor Ortho Biotech) and HUMIRA (adalimumab; Abbott) are well established, with respective revenues of $7.2 billion and $5.6 billion in 2009. The two other antibodies in this group that generated significant revenues, approaching $1 billion each, in 2009 were XOLAIR (omalizumab; Genentech/Novartis), for the treatment of asthma, and TYSABRI (natalizumab; Biogen Idec/Elan), for the treatment of multiple sclerosis.

The two other antibodies that generated significant revenues in 2009 were LUCENTIS (ranibizumab; Genentech) for the treatment of age-related macular degeneration and Synagis (palivizumab; MedImmune) for the treatment of respiratory viral infection, respectively $2.3 and $1.1 billion. Soliris (eculizumab; Alexion Pharmaceuticals), recently approved for paroxysmal nocturnal hemoglobinuria (which is a rare condition), managed to generate revenues of $387 million despite its use by a very small number of patients.

The development of new monoclonal antibodies for oncology indications is the area of greatest activity, with approximately 150 new monoclonal antibodies in clinical development for such indications. One of these, ipilimumab, was filed for approval for the treatment of melanoma in mid-2010, while four more are likely to be submitted for approval in 2011, with a further 11 in Phase III development. The most significant of these appear to be brentuximab vedotin for Hodgkin’s lymphoma, ramucirumab for, e.g., lung cancer, and Roche’s two antibodies to reinforce its Herceptin franchise.

A further 67 monoclonal antibodies are in Phase II for various oncology indications, with several highly promising antibodies scheduled to progress to Phase III in early 2011. Popular classes of targets are tyrosine kinase-linked receptors, chemokines, cytokines, cell adhesion molecules, and death domain receptors, while six radiolabeled antibodies and five conjugates with cytotoxic agents are also in Phase II. Myeloma, leukemias, and lymphomas are commonly the indications of choice. These indications and solid tumors are also among those most commonly indicated for the 66 antibodies in Phase I for oncology indications.

Some 70 monoclonal antibodies are in clinical development for the treatment of inflammatory and autoimmune diseases, 29 of which are being developed for the treatment of rheumatoid arthritis, psoriasis, or psoriatic arthritis. Other popular indications are asthma and the autoimmune disease systemic lupus erythematosus, for which no new treatment has been approved for many years. The majority of these monoclonal antibodies target a specific cytokine, with IL-13, IL-17, IL-5, and IL-6 all preferred targets, while chemokines and cell recognition molecules targeting either specific inflammatory mediators or cellular recognition pathways are also popular targets.

Nine of these antibodies are in Phase III development including belimumab and epratuzumab, which are being developed for the treatment of lupus. Belimumab is widely expected to provide a major clinical breakthrough in the treatment of this condition, with commensurate financial returns, and was filed for approval in 2010. Briakinumab was also filed for approval, for the treatment of psoriasis, but the applications were withdrawn in January 2011 pending further analysis. Of the other seven, the one that currently appears to have the greatest potential is vedolizumab, which is being developed for ulcerative colitis and Crohn’s disease, and which appears to lack the immunosuppressive effects of natalizumab.
Of the 32 monoclonal antibodies in Phase II for the treatment of inflammatory diseases, 16 are being developed (at least initially) for the treatment of rheumatoid arthritis, nine for asthma, and five for psoriasis. The majority of these are targeted against various cytokines. A further 29 antibodies are in Phase I development for the treatment of various inflammatory conditions, most commonly rheumatoid arthritis and systemic lupus erythematosus.

Just 68 monoclonal antibodies are in clinical development for other indications. Sixteen are in development for the treatment of various metabolic disorders, but one (teplizumab) of the two that had progressed to Phase III studies (in type I diabetics) is looking unlikely to progress further due to efficacy and side-effect issues, but current data with otelixizumab appear more promising. Two of the 16 antibodies in development for the treatment of CNS disorders are in Phase III studies. Both bapineuzumab and solanezumab target the β amyloid protein, but the former only showed modest effects in Phase II studies, suggesting that solanezumab may offer greater promise. Five other antibodies in earlier stage development are also targeted at β amyloid.

The commercial success of palivizumab appears to have been the stimulus for the development of antibodies targeting viruses and bacteria, with 25 antibodies in development for the treatment of infectious disease. Although December 2010 saw AstraZeneca abandon attempts to gain approval for motavizumab, both MK-3415A (for bacterially-caused diarrhea) and pagibaximab (for the treatment of Staphylococcal sepsis) are in Phase III development. A further ten antibodies are in development for the treatment of cardiovascular diseases or transplant rejection, but none have yet progressed to Phase III studies.

There remains scope for improving the therapeutic characteristics of monoclonal antibodies. Since injection is likely to remain the delivery route, the focus is on trying to ensure subcutaneous delivery, while minimizing injection-site events and the frequency of dosing. In addition, modifications to alter the therapeutic characteristics of the antibody remain a focus of activity. PEGylation is seen as one of the simplest methods of enhancing the pharmacokinetic properties of an antibody and altering its formulation properties. Therapeutic modification is being effected both by continued efforts on improving the design of antibody conjugates, especially with cytotoxic agents, and by fast-developing efforts on developing dual-specificity antibodies.

Seven major companies can be described as key players in the supply and development of monoclonal antibody-based products, each with 2009 revenues in excess of $1 billion from sales of antibody products. Roche dominated the monoclonal antibody market segment with a 46% share in 2009, while Abbott and Johnson & Johnson accounted for a further 25% market share. Roche’s dominant position has arisen through the pronounced success of three antibody products, each of which originated substantially or completely at Genentech. To follow these, it has an extensive development pipeline with four antibodies in Phase III and a further seven in Phase II development. Three of the four in Phase III seek to reinforce the franchise established with trastuzumab, while obinutuzumab has been designed to provide a different therapeutic profile than RITUXAN (although it targets the same antigen).

The success of adalimumab has seen Abbott become a commercially significant player in the antibody market, but its pipeline is modest, with only four antibodies in clinical development. Daclizumab is in Phase III for multiple sclerosis, while an initial filing for briakinumab (for treating psoriasis) has been withdrawn for additional data. Johnson & Johnson’s position is attributable to its acquisition of Centocor, but some of the
antibodies developed by the latter are marketed in some countries by Merck. Ongoing arbitration may rule in Johnson & Johnson’s favor and dramatically increase its revenues from such products. Two recent approvals have left the company with bapineuzumab as its only antibody in late-stage clinical development, for the treatment of Alzheimer’s disease, although eight or nine others are in Phase I or II development.

Merck currently commands a significant share of the monoclonal antibody market segment, almost completely due to revenues from REMICADE, but retaining these revenues is dependent upon a favorable ruling in the ongoing arbitration, which could see the marketing rights revert to Johnson & Johnson. Its pipeline is limited to three antibodies, with only MK-3415A, for the treatment of clostridium-induced diarrhea, in Phase III development. In contrast, Biogen Idec, with revenues derived from both RITUXAN and TYSABRI, has a much larger pipeline, but with most of the antibodies in Phase I. Both obinutuzumab, for leukemia, and daclizumab, for multiple sclerosis, are in Phase III development. Novartis currently generates revenues from three antibody products, with those produced by XOLAIR the most significant. Of the eight antibodies that Novartis has in development, it is the Phase III studies designed to extend the utilization of canakinumab to a major indication that are the most significant.

AstraZeneca’s successive acquisitions of Cambridge Antibody Technology and MedImmune established it as a major player in the development of monoclonal antibodies, with revenues currently derived solely from Synagis. However, with the abandonment of attempts to gain approval for motavizumab, none of its extensive pipeline is close to reaching the market. Seven antibodies are in Phase II, and a further seven are in Phase I studies. Other major companies currently derive (at best) modest revenues from antibody products, although several have made strategic acquisitions to enhance their pipelines of monoclonal antibodies and their capabilities to develop them. Recent significant acquisitions are of ImClone by Eli Lilly, Medarex by Bristol-Myers Squibb, Morphotek and Agensys by Eisai, as well as Facet by Abbott. Amgen has now established a large pipeline of antibody products, although none has yet followed (the now approved) denosumab to Phase III.

Smaller, technology-focused companies remain a major source of innovation in the antibody market, both for developing new technologies and as a source of antibodies for licensing deals. Most have antibody pipelines that are limited in size, but both Genmab and MorphoSys have been the source of multiple antibodies, most of which are currently being developed in partnership with major pharmaceutical companies. MorphoSys in particular has proved to be a highly successful deal maker, with its collaboration with Novartis yielding $600 million over a ten-year period; MorphoSys has also contributed to some 66 antibodies that are at various stages of development. Although Human Genome Sciences is the originator of the highly promising belimumab, it has only three other antibodies in development. UCB, one of the early leaders in the development of antibody technologies, has a limited pipeline of antibodies in development, focusing on extending the utilization of CIMZIA (certolizumab). Both ImmunoGen and Seattle Genetics have specialized in the development of antibodies conjugated to cytotoxic agents.

The general outlook for monoclonal antibodies is highly encouraging. They account for an increasingly high proportion of new therapeutic agents in development and are a major factor in the increasing proportion of biological agents amongst the approved new therapeutics. In 2009, three of the seven BLAs approved in the United States were for new monoclonal antibodies. In 2010, the three approved antibodies accounted for 50% of approved BLAs and 14% of all novel therapeutics approved.
Recent approval rates for monoclonal antibodies suggest that the period 2011–2015 should see around 15 new antibodies approved for use. At least 12 of these appear to have significant commercial potential, but it appears that the major commercial returns from monoclonal antibody products will probably be confined to the two therapeutic areas in which they are already well established.

Six new antibodies for the treatment of different cancers might reach the market by 2015. The overall impact of these new antibodies, allied to continued growth in sales of the established products, will see a steady growth in product revenues in the period 2010–2015. The value of the oncology antibody market segment should grow to $30–35 billion by 2015.

The commercial prospects for the anti-inflammatory segment of the monoclonal antibody market look good. Substantial revenue growth in the period to 2015 looks assured, driven by increased uptake of HUMIRA and some of the more recently approved antibodies. This will be accentuated by the introduction of antibodies for the treatment of lupus, especially belimumab, augmented by a number of other approvals. The collective impact of these developments should be the growth in revenue from this segment of the antibody market, with sales growing to around $35 billion by 2015.

Few, if any, of the antibodies in late-stage development for other indications appear likely to have a commercial impact by 2015. The likely abandonment of teplizumab, allied to the failure of motavizumab, leaves the possible approval of solanezumab as the best possibility of stimulating revenues in this segment of the antibody market. But with no filing likely before 2014, any impact will be modest.

Potential threats to the growth of the antibody market are reimbursement constraints, which may have an impact in some markets, and the potential introduction of biosimilar antibodies. Since patent constraints preclude their market entry before 2015, their impact will be negligible in the medium term. In 2010, global revenues from monoclonal antibody products will have moved significantly past the $40 billion level, and are poised to continue growing steadily through to 2015, when the overall value of the monoclonal antibody market should reach $70 billion.