BioSpectrum the business of Bio & Health Sciences

Monoclonal antibodies: A profitable segment

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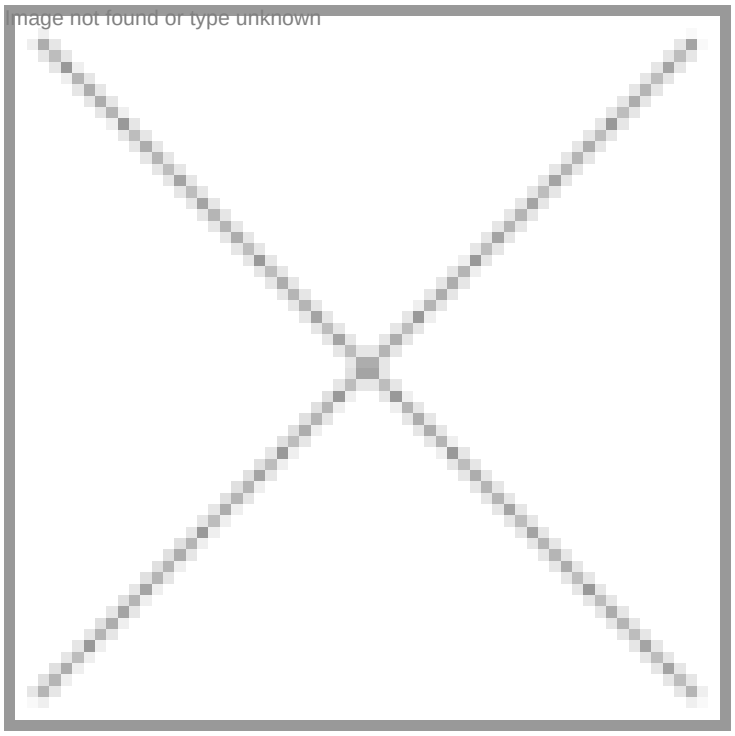

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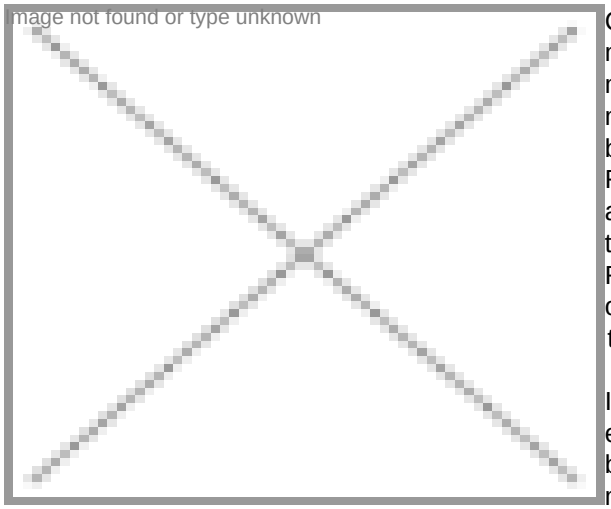


Companies all across the world are in pursuit of tapping the booming monoclonal antibodies market (mAbs). Between 2005 and 2008, the market witnessed an exponential growth wherein the global mAbs market more than quadrupled in just four years from Rs 31,101 crore ($7 bn) in 2004 to Rs 1.55 lakh crore ($35 bn) in 2008 with the 'Big Four'- Roche, Genentech (now a subsidiary of Roche) , Johnson & Johnson and Abbot leading the race. Therapeutic mAbs market is dominated by the 'Big Five' products-Avastin and Herceptin for oncology); Humira and Remicade for autoimmune and infectious disease (AIID); and Rituxan for oncology and AIID. In 2006, these products accounted for 80 percent of these products.

Industry experts are optimistic about the mAbs segment, which is expected to touch a compound annual growth rate (CAGR) of 14 percent between 2006 and 2012, surpassing growth rate of 0.6 percent in the more traditional, small molecules market. Dr Rustom Mody, chief scientific officer and director - quality, Intas Biopharmaceuticals, includes the Rs 44,430 crore ($10 bn) sales of mAbs for diagnosis and as reagents in research, so the market is worth Rs 2.22 lakh crore ($50 bn).

The boom in the mAbs segment is due to the increasing popularity of targeted therapeutic mechanism approaches among scientific community, particularly in disease segments like oncology and AIID. In case of cancer, conventional treatment of chemotherapy and radiation therapy, it often results in relapse and such patients ultimately die either from their cancer or due to toxicity levels of the therapy. The development of mAbs for these disorders have been studied to improve the therapies

and minimize the toxicities associated with standard therapies. MAbs are designed to demonstrate efficacy with low toxicity and are expected to reduce overall treatment and hospitalization costs associated with the side effects and opportunistic infections, which can result from chemotherapy or radiation therapy.

According to an independent market analyst, Datamonitor, with key individual mAb product franchises forecast to recordpeak sales growth through broadening horizontal indication and the launch of new products in the next few years, this rapid expansion is expected to continue. The commercial dominance of the big five is expected to continue till 2012, with the same products forecast to account for 70 percent of 2012 mAbs revenues. Datamonitor also predicts that Genentech/Roche will retain their dominance over the mAbs market till 2012, due to their ownership of three of the big five products. Oncology and AIID will remain the main focus areas for mAbs segment as they are the disease areas addressed by the 'big five'.

Industry analysts point out that new players such as Biogen Idec, Amgen, Novartis and UCB Pharma, Bristol-Myers Squibb and Sanofi-aventis will expand their presence in the mAbs market by 2012.

Growth demand for mAbs

With dwindling R&D pipelines, patent expiration of blockbuster products, and apprehensions over subsequent dip in revenues till 2012, most pharmaceutical companies have chalked out a 'mAbs strategy'. This was evident from a spate of licensing deals between pharma and biotech companies in the mAbs space and a spree of biotech firms being acquired by pure pharma companies in the recent past. In 2006, GSK etched a mark with the company licensing a drug for leukaemia from Genmab for Rs 9,341 crore ($2.1 bn), the largest ever deal in terms of value in the mAbs segment. The year 2009 saw some mega mergers with the Roche-Genentech deal gaining the center of attraction.

â€œMAbs offer an enormous amount of target specificity that reduces the nonspecific, untoward side effects commonly observed in small molecules. Many companies across the globe have mAbs products in advanced clinical trials stage,â€? says Dr Mody. Cancer and anti-infammatory segments contribute 51 and 30 percentages respectively, according to a report by Datamonitor and Frost & Sullivan.

Experts from the scientific community point out that human mAb has a higher rate of technical success and negligible levels of toxicity and lesser degrees of side effects. â€œThe platform technology can easily be adapted for novel mAbs as the variability that can be introduced within the antigen-binding domains of mAbs increases their molecular diversity and extends the range of potential therapeutic applications,â€? says Dr Mody.

On the international front, numerous factors have motivated the companies to opt for mAbs. There has been an upsurge in demand for mAbs products because very few chemical-based products are available to provide effective cure for diseases such as cancer, asthma, anti-inflammatory, osteoporosis and opthalmology. â€œChemical-based products have failed to provide remedy for oncology diseases. The technological competency of mAbs helps to get rid of these diseases,â€? says Sujay Shetty, associate director of pharmaceutical and lifesciences, PricewaterhouseCoopers India.

The commercial success of blockbuster products like Avastin and Herceptin for oncology; Humira and Remicade for AIID; and Rituxan for both oncology and AIID, has been a stimulus for the companies rolling out a large number of R&D projects in mAbs. Remicade has been the best selling antibody since 2004 and was the market leader with sales of over Rs 28,915 crore ($6.5 bn) in 2008, followed by Rituxan, Avastin, Herceptin and Humira. The first three products made it to the top ten and all five products made it to the top 20 global best selling human medicinal brands. Till 2008, there were over 200 antibodies out of 630 biologics in clinical trials testing for cancer, arthritis, infections, asthma, macular degeneration, osteoporosis, diabetes and other chronic diseases. Increased sales and profitability have attracted mainstream pharmaceutical companies towards mAbs. The pressure of pricing is much lower in this space.

In India, the demand for mAbs is increasing and there is an upsurge in the number of Indian companies venturing into this space. India has capitalized on its so-called 'low cost destination' advantage. â€œHuge investment is needed to establish large scale manufacturing facilities for mAbs. The fund needed for setting up large scale operations is still lower in India as compared to developed markets. By establishing their operations in India those developed markets can fulfill their growing demand for mAbs products. India offers the possibility of improving their profit margins,â€? says Dr Mody . Biocon and Dr Reddy's Labs, two of India's top life sciences companies, have already launched their products in the market successfully.

The latest debate among the biotech circles are the opportunities that biosimilar mAbs has to offer to companies. The global biosimilars market is primarily dominated by three main components â€“ mAbs, therapeutic proteins and vaccines. In 2009, 29 mAbs were approved and marketed for therapeutic use. With the patent expiry of products like Herceptin, Humira and Rituxan by 2020, generic versions of these products are in the pipeline of many Indian players. Analysts predict that it will be a tussle for dollars for Indian players in the coming decade. Currently there are about 25 Indian companies operating in the space bringing out at least 40 products in the market and many of them are well positioned to compete in the global mAbs

landscape. â€œThis product class is gaining maturity and within five years, when the second wave of biologicals are going to be off-patent, many of which are blockbuster mAbs, India is likely to dominate biosimilar mAbs development and manufacturing,â€? adds Dr Mody.

In terms of funding, venture capital firms are optimistic about mAbs space. â€œGlobally, venture capitalists are willing to invest in two areas â€“ interferons and mAbs,â€? says Shetty The main reason for this is the patent expiry of mAbs worth Rs 47,154 crore ($10.6 bn) by 2018. MAbs is the focus area for many pharma and non-pharma companies and hence R&D, M&A and licensing deals are happening in billion dollars for this class of products. A venture capitalist from a leading firm in India told BioSpectrum (without mentioning any names) that he was aware of many reputed VC firms (which includes his firm) in India are looking at investing in mAbs space in the event of a rising number of Indian companies venturing into the segment.

mAbs in India

Biocon was the first Indian company to come up with its mAbs product, BIOMAb-EGFR, and the product was granted regulatory marketing and manufacturing approval in India in September 2006. The product is a therapeutic monoclonal antibody-based drug for treating solid tumors of epithelial origin, such as head and neck cancers. This novel drug is engineered to specifically target and block the epidermal growth factor receptor (EGFR) responsible for the proliferation of cancer cells. Dr Harish Iyer, R&D head, Biocon, â€œAs far as Biocon's portfolio is concerned, we have one product in the market from our stable.

BIOMAb EGFR (Nimotuzumab) is a monoclonal antibody that specifically binds to the extracellular domain of EGFR and prevents signal transduction. It is used in the treatment of advanced squamous cell carcinoma of the head and neck region with concurrent chemotherapy and/or radiotherapy.â€? It is also being globally studied in a range of solid tumor types, including colorectal cancer, lung cancer, glioma and pancreatic cancer. â€œBiocon has also partnered with Mylan for co-developing biosimilar mAbs. This is a co-development, cost sharing agreement for a bunch of molecules that are currently in development,â€? says Dr Iyer.

Apart from being a low cost manufacturing destination, Indian companies have the upper hand of offering mAbs products at comparatively lesser price margins. At the launch of BIOMAb -EGFR, Dr Kiran Mazumdar-Shaw, chairman and MD of Biocon, said, â€œBIOMAb -EGFR is competitively priced to make cancer treatment more affordable. â€œIn 2007, Dr Reddy's Labs came out with the novel concept of producing the biosimilar version of Rituximab, a version of Roche's cancer therapy, which could allow a greater access to the drug at half the price of the original. With the more complex molecules like mAbs, Dr Reddy's believes that the preferred strategy is to systematically develop the entire spectrum of development and manufacturing capabilities. The complexity of the molecules and the processes means a close integration of all the relevant skills within one organization with direct links between the manufacturing groups and the process, analytical, pre-clinical and clinical development groups. World-class facilities and laboratories of Dr Reddy's, the scientific depth of its team, the robustness of the development strategy and the focus on quality issues were some of the key factors that contributed to the successful development of a complex molecule like Reditux.

Reditux is the second product from Dr Reddy's Biologics Division, which is developing treatments for cancer andautoimmune diseases. The company has also launched the generic version of Amgen's Neupogen, and named it Grafeel. The company has spent more than Rs 44.48 crore ($10 mn) for developing Reditux and within a year of its launch the products have successfully gained 30-35 percent share of the market. Dr Reddy's Reditux is priced at Rs 39,996 for a vial and is almost half the price of Roche's Mabthera. This product is now approved for marketing in India.

Pune-based Serum Institute has entered into another agreement with Akorn of the US in 2007 for definitive developmentand exclusive distribution rights for rabies mAb. As part of the agreement, Serum has agreed to appoint Akorn as the exclusive distributor for rabies mAb. In exchange for Akorn receiving the exclusive marketing and distribution rights of North, Central, and South America, Akorn has agreed to provide Serum funding for product development through milestone payments.

Intas Biopharmaceuticals has signed a Memorandum of Understanding (MoU) with Government of Gujarat in 2009 forsetting up a separate manufacturing facility for MAbs, a recombinant mammalian platform product. The company will invest Rs 160 crore towards setting up a manufacturing facility at Sanand near Ahmedabad. The facility, fully-dedicated for mAbs, will undertake large-scale manufacturing of the recombinant product with a capacity of 5000L in phases. â€œAs part of its Strategic Research Initiative (SRI), the company is focusing on cloning mAbs and developing proprietary and novel expression systems using different mammalian cell lines,â€? says Dr Mody.

These companies apart, Daftary group promoted Bharat Serums and Vaccines and Bangalore-based Avesthagen are some

of the other notable companies that have chalked our serious plans for the space.

Challenges ahead

MAbs are complex protein molecules. In addition to the protein structure, often there is a carbohydrate moiety attached tothe molecule. Characterization of such complex molecules is a challenge, this is why, very few companies in India are active in mAbs arena. â€œNot only do you need sophisticated equipment to analyze mAbs, you also need skilled manpower to do this. Since most of these are immune-modulatory in nature, they have complex reactions with the human body.

Therefore, we have to determine the biological activity of these molecules using specific cell lines. Performing suchbioassays is also a challenging,â€? adds Dr Iyer.

Industry experts agree that the mAbs market in India is in its nascent stage. In India, only few players are active in mAbs space. There are many players who have aspirations to enter the space as the next generation of biotech products would be mAbs. However, there are only a handful of companies that have products in the preclinical stage.

The reasons are many. â€œIt is difficult to copy human mAbs, which is complex and expensive process. It takes a long time to develop and it needs some vigorous ground work and intensive research that Indian companies are yet to gain mastery,â€? adds Shetty.

In addition to this, the Drug Controller General of India (DCGI) is yet to come out with a set of systematic guidelines dedicated especially for mAbs. Companies like Dr Reddy's Labs and Biocon have been the only two companies successful in bringing in products while the remaining are still in the development stage.â€?Shetty says, â€œIt will take some time for India to become a lucrative market for mAbs. In biogenerics, too, the market would take time to pick up. In addition to this, the high costs of investments involved can also be a barrier.

â€œMAbs business involves patents and for navigating through these patents requires exceptional skills,â€? adds Dr Mody.

Future prospects

By 2015 , due to the expected launch of many new therapies such as Denosumab and Teplizumab, the sales of mAbs is expected to reach Rs 3 lakh crore ($67.6 bn), with a CAGR of 13.8 percent between 2008 and 2015. The biotherapeutic market would be dominated with mAbs in next five years as most of the blockbuster molecules are going off-patented.

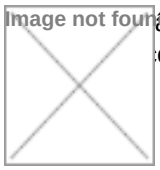
All the pharma majors have mAbs projects in their R&D portfolio. Introduction of newer monoclonal antibodies will greatly expand the market. Globally, the FDA had approved four new mAbs and EMA had approved seven new mAbs in 2009. There were at least six new mAbs under regulatory review, 26 mAbs (32 in 2008) are in phase III and over 100 are in phase II clinical trials. There are more than 150 mAbs molecule awaiting regulatory approval. In addition to this, several promising candidates from companies like Pfizer are in phase III clinical trials.

In the recent past, Sanofi-aventis Chris Viehbacher, CEO of Sanofi-aventis, had commented that they had missed the 'boatto biologics' and are in active pursuit of this promising mAbs market. Sanofi-Aventis is converting a factory near Paris into a biotechnology development hub, with its doors wide open to smaller biotech companies looking to partner on projects. The French pharma giant says that the Rs 1,178 crore ($265 mn) venture marks their commitment to ramping up their work on biologics. It is an opportunity for the company to do partnerships with biotechnology and research companies. The investment of nearly Rs 1,183 crore (â‚¬200 mn) will give rise to the first cell culture biotechnology platform of the group to produce mAbs from 2012.

On the other hand, within the same time period, experts are cynical as to whether India can match up to global standards given a the huge amount of investments and the complexity that the process involves. â€œI do not see that Indian companies achieving much by 2015 and taking their products globally is but a distant dream,â€? concludes an analyst.

Compared to India, China is a big market for mAbs. Some notable companies include Union Stem Cell and Gene Engineering and Biotech pharmaceutical. In a serious effort towards innovation,China is moving towards areas like stem cells, mAbs, cancer and HIV development and vaccines with investments being pumped in both by the Government and foreign sources. India, experts opine needs exactly the same kind of backing if it need to bolster growth rates of the sector in

the region.



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Mody, chief scientific officer and director-quality, Intas Biopharmaceuticals

Nayantara Som with inputs from Jahanara Parveen