Biosimilar Monoclonal Antibodies in the Pipeline: Major Players and Strategies

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One of the biggest challenges facing biosimilar drug developers is proving the equivalence or similarity of their biological drug to the reference product. This is particularly difficult in the case of monoclonal antibodies (mAbs), which vary greatly in properties and where even small alterations can lead to unacceptable changes in safety and efficacy. As is the case with biosimilars in general, the guidelines for the development of biosimilar forms of mAbs are better established in the European Union than they are in the US. However, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) announced in June 2011 that they have set up a mechanism to exchange information on biosimilars, which will help the US move forward in developing guidance, as well as provide a worthwhile conduit of information in both directions.

Despite the challenges associated with the development of biosimilar drugs, many drug manufacturers are entering the race to develop biosimilars, especially for blockbuster mAbs . Two biosimilar mAbs are already launched, Dr. Reddy's rituximab, Reditux was approved in India in 2007, and Clotinab, ISU ABXIS' biosimilar form of abciximab is launched in 30 countries worldwide, including the US and EU. In addition, according to Citeline's Pipeline database there are currently 49 biosimilar mAbs in the pipeline based on information that has been released in the public domain. The vast majority of these mAbs (43) are in preclinical development, and 6 are in phase II or phase III development. With so many mAbs in such early stages of development, and considering that a number of mAbs previously developed by pharmaceutical companies will be losing patent protection over the next few years, the time is certainly opportune for entry into the marketplace for drugs of this therapeutic class.

Who are the major players in the development of biosimilar mAbs?

As shown in Table 1, BioXpress of Switzerland has 16 mAbs in preclinical development, with 6 being targeted to oncology indications and the remaining in autoimmune/inflammation, metabolic, infectious disease and central nervous system

indications. The company has disclosed that it is developing biosimilar versions of several oncology mAbs including alemtuzumab, bevacizumab, ofatumumab, panitumumab, ritixumab and trastuzumab. mAbs currently in development in other therapeutic areas include adalimumab, ustekinumab, tocilizumab, omalizumab, natalizumab and infliximab (autoimmune/inflammation), pavlivizumab for infectious disease indications, natalizumab for CNS disorders and denosumab for metabolic disorders.

Following closely is Japan's GeneTechno Science with 6 undisclosed mAbs across several therapeutic areas and India's Zydus Cadila with 5 undisclosed mAbs in development for various oncology indications. The remaining biosimilar mAbs are being developed by companies that each have one or two in the pipeline, with the majority being at the preclinical stage, and just a handful that are further along in development.

Table 1: Biosimilar mAbs in the Pipeline*

Company	Location	# Biosimilar Mabs	Highest Development Status
BioXpress	Switzerland	16	Preclinical
Gene Techno Science	Japan	6	Preclinical
Zydus Cadilla	India	5	Preclinical
PlantForm	Canada	3	Preclinical
BioCad	Russia	3	Preclinical
Celltrion	South Korea	2	Phase 3
LG Life Sciences	South Korea	2	Preclinical
Gedeon Richter	Hungary	2	Preclinical
Cerbios-Pharma	Switzerland	1	Preclinical
Hanwha Chemical	South Korea	1	Preclinical
PharmaPraxis	Brazil	1	Preclinical
Probiomed	Mexico	1	Phase 3
Samsung BioLogics	South Korea	1	Preclinical
Novartis	Switzerland	1	Phase 2
Teva	Israel	1	Phase 2
Zenotech	India	1	Phase 3
Spectrum	US	1	Preclinical
Biocon/Mylan	India/US	1	Preclinical

*as of September 10, 2011 from Citeline's Pipeline database

Strategic Decisions: Sharing expertise vs going solo

Of interest to note are the strategies that companies are using to join the race to develop

biosimilars. Interestingly, only a few of the companies with mAbs in preclinical development have announced partnerships or licensing deals. Gedeon Richter, located in Hungary, and Stada of Germany announced a licensing deal at the end of August 2011 giving Stada non-exclusive distribution rights for Europe and the Commonwealth of Independent States, excluding Russia, for biosimilar forms of rituximab and trastuzumab. Development of rituximab, which is at the preclinical stage, and trastuzumab, which was discontinued during preclinical development by Stada in 2010 for strategic reasons, will now be continued by Gedeon Richter.

Meanwhile, Celltrion in South Korea is in phase 3 with both trastuzumab and infliximab, and has licensed both of these to Nippon Kayaku for development in Japan. Zenotech of India, which is in phase 3 with a biosimilar form of rituximab for Non-Hodgkin's Lymphoma (NHL) was recently acquired by Japan's Daiichi Sankyo. Probiomed of Mexico is also in phase 3 with a biosimilar of rituximab for NHL , but does not have any partnering or licensing opportunities at present. While both Novartis and Teva are in phase 2 with a biosimilar form of rituximab for the treatment of rheumatoid arthritis, Teva is also developing rituximab for treatment of NHL.

What is apparent from the Citeline data is that with the majority of biosimilar mAb development at the preclinical stage, the opportunities for partnerships and licensing deals are plentiful. Collaboration will be an important strategy for overcoming some of the difficulties associated with the development of biosimilars. There is a great deal of complementary expertise among smaller firms specializing in biosimilar development and production and larger pharmaceutical and biotechnology companies that have the resources to run trials, submit filings and market drugs. By collaborating with the right partners, firms can leverage this varied expertise to best meet the specialized challenges of developing and marketing biosimilar mAbs. There are also opportunities for other types of organizations such as CROs and consulting firms to become involved and lend their expertise in clinical trials planning and regulatory strategy, as evidenced by the recent joint venture between Merck and Paraxel to form Merck Bioventures, a firm dedicated to developing biobetters as well as biosimilars.

mAb biosimilars represent a large portion of all biologics in development

The Citeline data shows that by comparison, monoclonal antibody biosimilars comprise quite a large proportion or approximately 25% of what is currently in development for biosimilars across all therapeutic classes. This is consistent with figures posted in a report by the Generics and Biosimilars Initiative on May 6, 2011 stating that

approximately one third of all biological drugs currently in development are mAbs. Whether this means we will see a large influx of biosimilar mAbs entering the marketplace in the coming years will depend on many factors, including whether the difficulties associated with developing these drugs can be overcome and development can proceed in a cost-effective manner.

European and Asian companies take the lead with better guidance

Geographically, the majority of development is taking place equally in Europe and Asia. Very little is happening in the Americas, as only 6 of the 49 mAbs in the pipeline are being developed by companies in these areas. Most notably absent in the development of biosimilar mAbs are US companies. This may be a consequence of the lack of guidance in the US, although a recent article by FDA officials in August 2011 in the *New England Journal of Medicine* stated that guidance should be released by the FDA at the end of this year. With all of the uncertainty in development and reporting guidelines, some companies may not be disclosing biosimilars monoclonal antibody development at this time.

North American companies focused on biobetters

Not everyone is joining the biosimilars race. Some are choosing instead to focus on developing biobetters, which are intended to improve upon the original molecule by increasing safety, half-life or overall efficacy of the drug to compete with the biosimilars marketplace. As far as mAb biobetters are concerned, BiOasis of Canada is currently in preclinical development with a biosimilar form of trastuzumab, BT-2111. This mAb is conjugated to the Transcend delivery vector, designed to cross the blood-brain barrier, for treatment of brain metastases from primary breast cancer.

While not so well represented among companies developing biosimilar forms of mAbs, US based firms appear to be gearing up for development of biobetters. In March 2011, a collaboration was formed between US based ProtevoBio and A-CUBE to develop biobetter mAbs combining wet lab technology for antibody engineering and design capabilities using algorithms. In May 2011, GTC Biotherapeutics was granted patent protection on their transgenic protein production, allowing them to move forward with developing biobetter mAbs. Charles River Laboratories, a US company that offers a variety of preclinical services has disclosed that some of its clients include biotech firms focused on the development of biobetters. Certainly, development of conjugated and modified forms of mAbs will require a concerted effort by companies specializing in

various in-silico and laboratory technologies and should benefit greatly from increased collaboration.

Stay tuned – Many new developments are yet to come

In the months and years to come, it will be interesting to watch the various strategies used by drug companies to enter into development of biosimilars and see which ones will prove the most successful for competing in the marketplace. With the release of biosimilars guidance by the FDA at the end of 2011 giving the details of the approval pathway in the US, as well as collaboration between the EMA and FDA, it is predicted that more US based firms will enter into the race to develop biosimilar mAbs. With so many of these in early phase development and with the flurry of activity in biosimilars in general, it is encouraging to think that all of this will contribute to a more successful era of drug development focused on unique collaborations, cost-effectiveness, and with the development of biobetters, therapies that are also safer as well as more efficacious.
