The next 10 years should be a golden age for the Chinese biologics industry

China: the Next Frontier for Biologics

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Led by development of monoclonal antibodies (mAbs), the biologics industry has witnessed phenomenal growth in the past 20 years. The emergence of mAbs has produced significant breakthroughs in the treatment of cancer and autoimmune diseases. In 2015, seven of the top 10 best-selling drugs were biologics, including six mAbs.[1] Recently approved immuno-oncology mAbs such as Keytruda (pembrolizumab) and Opdivo (nivolumab) and an exciting immuno-oncology pipeline are set to drive the growth of antibody therapeutics in the years to come.

In 2014, the mAb industry accounted for $68 billion in global pharmaceutical sales. By contrast, total mAb sales in China were merely $0.9 billion, despite over 40% average growth during the past 5 years.[2] MAb treatments for autoimmune diseases accounted for 20% of global biologics sales, but only 4% in China.[3] In China, expensive treatments—including mAbs—are usually paid by patients out-of-pocket, so affordability is a major challenge in adopting these new medicines.

China's outdated regulatory system, designed mainly for small-molecule generics, has not been able to provide the necessary support for innovative products from either domestic companies or multinational corporations. It is estimated that new products are typically launched in China 5–9 years later than in the United States. Approximately 30% of US-approved cancer treatments, for example, are not yet available in China. Availability of these novel treatments poses another significant challenge for the Chinese pharmaceutical industry.

As China is the largest developing country with a dramatically aging population, the need for new medicines to treat cancer and other diseases is becoming urgent. Regulators, the pharmaceutical industry, and policy makers are working together to address both affordability and availability of these new medicines—especially mAbs.

CFDA guidelines

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The first wave of changes came from recent top-down regulatory reforms. In March 2015 the China Food and Drug Administration (CFDA) published its first guidance on the development and evaluation of biosimilars, which is much welcomed and puts an end to many discussions and debates over whether biosimilar standards in China should be consistent with global guidelines. It is anticipated that biosimilar companies in China will now adapt quickly to develop biosimilars to global regulatory standards. Thus, select companies in China may play expanding roles in the development and introduction of biosimilars to the global drug market.

Besides issuing the biosimilars guideline, the CFDA also implemented major reforms to drive innovation. In February 2016, the agency announced comprehensive overhauls and stated that it would give fast-track status to innovative products that fill the gap of unmet medical or clinical needs in the country. Equally important, the agency plans to significantly reduce Investigational New Drug (IND) application review time. This is expected to reduce IND review for oncology products from 18–24 months to 2 months, and closely align CFDA review process with other global regulatory agencies. These reforms will generate great excitement from the Chinese biotech industry to develop both biosimilar and innovative biologics.

To address the affordability of biologics with no or expired patents, a cluster of domestic companies are focused on the development of biosimilars. Due to limited resources in talent, good manufacturing practice, manufac-



turing to global regulatory standards, and financial support, as well as the lack of return in the near-term, Chinese companies naturally selected biosimilar investments that generate potentially higher returns with lower risk.

Booming biopharmaceuticals

Per Reuters' reports, China now boasts the second-highest number of biosimilars in development after the United States. As of April 2016, it is estimated that 27 companies are developing a biosimilar to Humira (adalimumab). Alphamab, a Suzhou, China–based biologics drug company, claimed to have 28 biosimilar programs in development (the most in China), followed by Qilu Pharmaceuticals with 10 programs.[4] Many of these companies are collaborating with global contract research organizations (CROs) to gain access to high-producing cell lines and deep process knowledge to leverage the CROs' integrated talent, technology platforms, and research and manufacturing facilities, in addition to minimizing upfront financial investment (Table A).

This biosimilar development is a direct reflection of China's booming biopharmaceutical industry. China-based biosimilar developers are expected to compete fiercely with global companies to drive down treatment cost; this will somewhat address the affordability challenge in China. If history can repeat itself, current development of mAb biosimilars could mimic biosimilar erythropoietin (EPO) and human growth hormone (HGH) development in China in the 1990s, where more than 20 companies had products on the market and pricing was driven down by over 60%. As a result, the Western EPO and HGH innovator companies gave up the Chinese market to these domestic companies and today, after continued intense competitive pressures, four or five local companies now dominate the Chinese market for these drugs.

There are also three biosimilar versions of Enbrel (etanercept) approved in the Chinese market, which are priced at 30%–50% of the originator product. The domestically manufactured etanercept generated approximately $113 million sales in 2014, accounting for approximately 62% of Chinese market share. This suggests that with a sound biosimilar strategy both Chinese biosimilar developers and foreign companies aiming for the Chinese biosimilar market can be successful and at the same time help drive down health care costs in China (Table B).

Strategic pillars

Since 2012, the Chinese government has named the biopharmaceutical industry as one of seven "strategic and pillar industries." The government created mega research grants with an average $1 billion per year to support of technology platform development that will spur pharmaceutical innovation. The class of anti-programmed cell death protein 1, (anti-PD-1) mAbs and antibody-drug conjugates (ADCs) were listed as separate megaprojects.

As a result, there are already five companies with novel anti-PD-1 mAbs filed with the CFDA for clinical trial approval or in Phase I trials. In December 2015, China's very first anti-PD-1 antibody by Shanghai Junshi Biosciences was approved for clinical trials by the CFDA, almost at the same time as Bristol-Meyers Squibb's anti-PD-1 mAb Opdivo. Throughout China an additional 15 anti-PD-1 or anti-programmed death-ligand 1 (anti-PDL-1) programs are in preclinical development. It is hoped that this strong support for both local innovation in China and global innovation worldwide will gradually address China's availability challenge by bringing in novel biologics to treat diseases in patients who need them most (Table C).

Table A: Biosimilars in development by Chinese companies[5]

Name	Brand Name	Chinese Biosimilar Development Projects
Adalimumab	Humira	27
Bevacizumab	Avastin	18
Etanercept	Enbrel	15
Infliximab	Remicade	13
Rituximab	Rituxan	25
Trastuzumab	Herceptin	24

Table B: 2014 Tumor necrosis factor blocker sales in China[6]

Brand Name	Biosimilar	Company	2014 Sales
Etanercept	Yisaipu Qiangke	3S Bio (CPGJ) Shanghai Celgen	$113 million
Enbrel	Etanercept	Pfizer	~$10 million
Remicade	Infliximab	Janssen	~$50 million
Humira	Adalimumab	Abbvie	~$10 million

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One of the reasons the market space in biosimilars and anti-PD-1 mAbs is so crowded is that the Chinese pharmaceutical market is still fragmented by the types of drug bidding and insurance plans provided by each province. It is possible that any company could have a strong hold in one or several provinces. In addition, a local Chinese biologics company only needs to receive approximately 15%–20% market share to be profitable, due to the lower cost basis and lower margin expectations. This crowdedness will not disappear until the Chinese pharmaceutical market consolidates and several dominant companies emerge.

Golden age

With innovation in great demand, Chinese companies are also looking abroad to beef up their biologics pipelines quickly—and to some extent more cost-effectively. Table D outlines recent cross-border deals focusing on innovative biologics. Most companies are sourcing innovation from the United States, Europe and South Korea. In particular, there are several interesting and complementary collaborations between Korean and Chinese companies. Korean companies tend to invest more in research and early discovery, while Chinese companies consider development and manufacturing as their core expertise. A number of cross-border biosimilar deals were also recently announced. This trend is expected to continue at an even faster pace as companies continue to invest in biologics in China.

Table C: Anti-PD-1 mAbs pending IND approval or in clinical trials[7]

Official Name	Sponsor	Status
Nivulomab	Bristol-Myers Squibb	Phase I clinical trial
Pembrolizumab	Merck Sharp & Dohme	Clinical trial application filed
Humanized PD-1 mAb	Junshi	Phase I clinical trial
Humanized PD-1 mAb	Hengrui	Phase I clinical trial
Humanized PD-1 mAb	BeiGene	IND filed
PD-1 mAb	Genor	IND filed
Fully human PD-1 mAb	Gloria	IND filed

Besides sourcing innovation abroad, local innovations are bubbling, and several collaborations with US companies have been announced, as well: Innovent–Eli Lilly and Hengrui–Incyte partnerships are centered on anti-PD-1 mAb assets available from Chinese companies. Interestingly, a third such partnership between Merck Sharp & Dohme and Akeso Bio also

Table D: International collaboration in innovative biologics[8]

Licensee	Licensor	Licensor Region	Product
Simcere	Apexigen	USA	VEGF mAb
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Zhejiang Medicine	Ambrx	USA	HER2 site-specific ADC (ARX-788)
Eddingpharm	Prima BioMed	EU	LAG-3-Fc fusion protein
3S Bio	PharmAbcine	Korea	Tanibirumab
Chemo Wanbang Biopharma	Genexine	Korea	EPO-HyFc (GX-E2)
Jinghua	Kadmon	USA	Fully human PDL-1 and VEGFR2 mAbs
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Beike Biotech	Altor Bioscienes	USA	Immunotherapy
Galaxy Bio	Oncoimmune	USA	Immuno-oncology portfolio including CTLA4 mAb
Zai Lab Ltd	UCB	EU	Undisclosed first-in-class autoimmune program
CANbridge	APOGENIX GmbH	EU	CD95R Fc fusion protein
Tasgen	Genexine	Korea	A portfolio of five products
CANbridge	Aveo	USA	HER3 mAb
Shutaishen	InflaRx	EU	Novel infectious disease target

Table E: Chinese companies' biologics out-licensure or codevelopment partnerships[9]

Licensee	Licensor	Product
Eli Lilly and Company	Innovent	Anti-PD1 mAb and bispecifics involving anti-PD1 mAb
Incyte	Hengrui	Anti-PD1 mAb
Merck Sharp & Dohme	Akeso Bio	Immuno-oncology mAb

focused on another immuno-oncology asset. All three innovations were originally derived from global CROs, indicating strong global CRO–biologics company partnerships in China (Table E).

Although there will be plenty of challenges, the next 10 years should be a golden age for the Chinese biologics industry, both in terms of innovative biologics and biosimilar mAbs. With investment pouring in, the regulatory process bottleneck expected to disappear, and private insurance emerging to pay for expensive biologics, entrepreneurship in China is poised to become wildly successful. This, in turn, could trigger even more excitement for the biologics industry. It is not surprising that IMS Health predicts that China could be the world's second-largest biologics market by 2020.[3]

China *is* the next great frontier of the biologics industry! ■

China's biosimilar development is a direct reflection of its booming biopharmaceutical industry

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