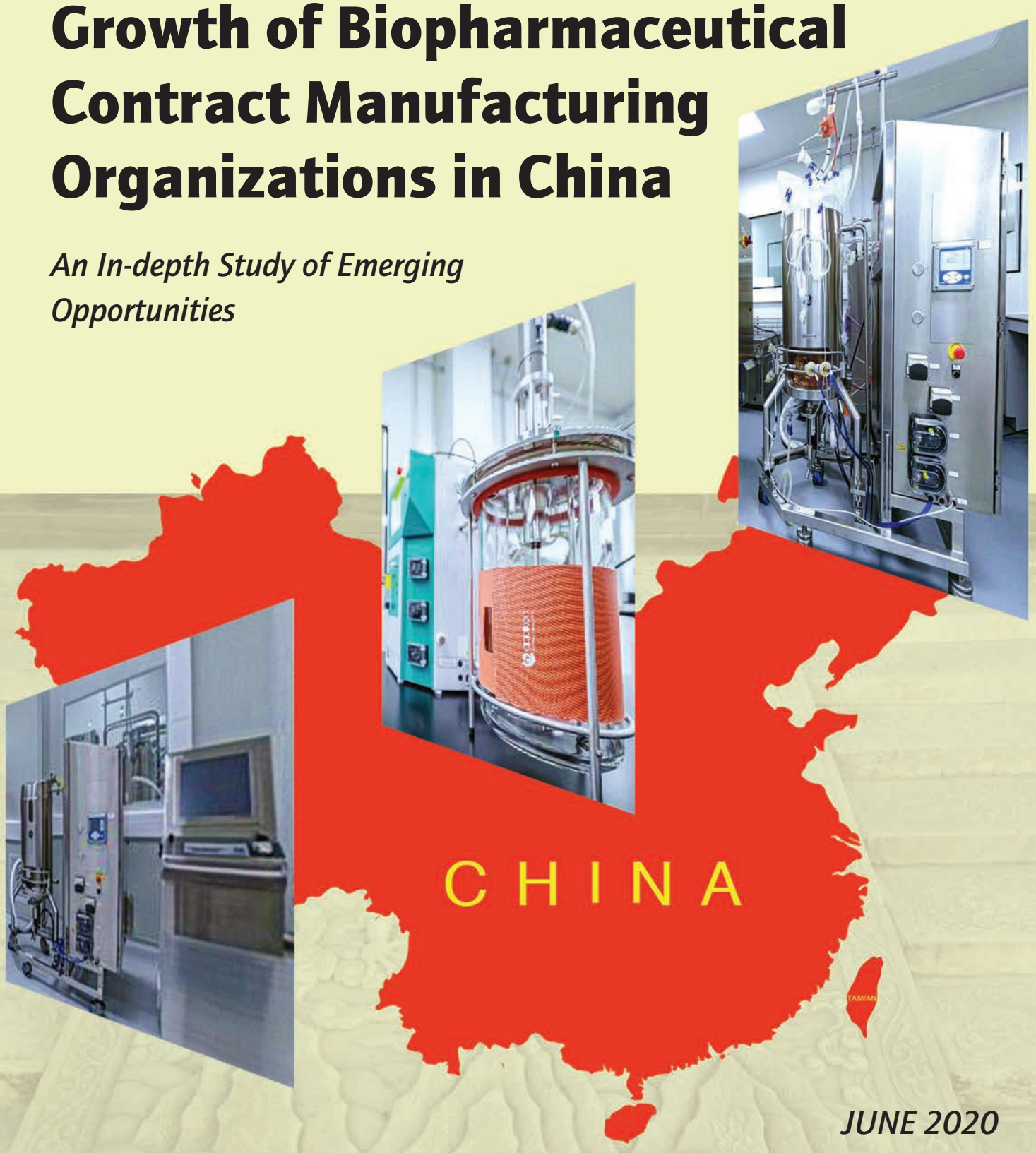
BioPlan associates, inc.

Growth of Biopharmaceutical Contract Manufacturing Organizations in China

An In-depth Study of Emerging Opportunities



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ABOUT BIOPLAN ASSOCIATES, INC.

BioPlan Associates, Inc. is a biotechnology and life sciences market analysis, research, and publishing organization. We have managed biotechnology, biopharmaceutical and life sciences research projects for companies of all sizes for over 30 years. Our extensive market analysis, research and management project experience covers biotechnology and biopharmaceutical manufacturing; vaccines and other biopharmaceuticals development; contract research services; biotechnology supply, and testing and R&D laboratory activities.

We prepare custom studies, and our publications provide public information our clients require to make informed strategic decisions, define objectives, and identify customer needs. With market and strategic information, our clients and publication readers are better able to make informed, market-based decisions because they understand the trends and needs in high technology life sciences industries.

BioPlan Associates, Inc. has researched global growth opportunities in the biopharma industry since 1989, and we have researched China market segments since 2004. Our work includes publications such as our peer reviewed studies, *Advances in Biopharmaceutical Technology in China,* our China biopharma facilities and services directories, distributor reports, and contract research analyses. BioPlan's staff in China have decades experience in providing quantitative and qualitative research projects, and strategic opportunities analysis. For further information, please contact us.

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PREFACE

BioPlan Associates' report on the China Contract Manufacturing Organizations (CMOs) industry cover regional industry developments, regulatory and legal changes, and reviews China's major CMO and CDMO companies with facility information, company ownership, background, management and facility capacity and history. This study is based on in-depth research, using public secondary and primary information resources. This is an on-going project that will be updated in the future to provide trends information, and relevant new in-depth insights into the rapidly growing and changing Chinese biologics industry.

As the Chinese industry continues to expand, both in technical capabilities and commercial presence, the information in this directory will, necessarily, become outdated. As such, we will have on-staff researchers to keep it up-to-date. However, our readers' input will be invaluable in that regard. If you have comments or corrections, please forward them to us.

The review and rating of companies in this study are based on information publicly available. Factors such as liters' capacity, number of employees related to biologics production, number of products in commercial or clinical production and financial estimates in some cases are derived from other available data. Because the Chinese biopharmaceutical contract manufacturing industry is in a growth phase, some of the organizations profiled are emerging entities, and have been included because, based on their internal expertise, or financial backing, may have the potential to rapidly enter this market with their own biological products.

We wish to acknowledge the contributions of our reviewers who have compiled and evaluated the content of this directory. Without their support, this project would not have been possible.

Exchange Rate: 1 dollar = 7 RMB, 1 dollar = 7.75 HK$ (May 2020)

Vicky Qing Xia
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June 2020

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CONTENTS

FIGURES

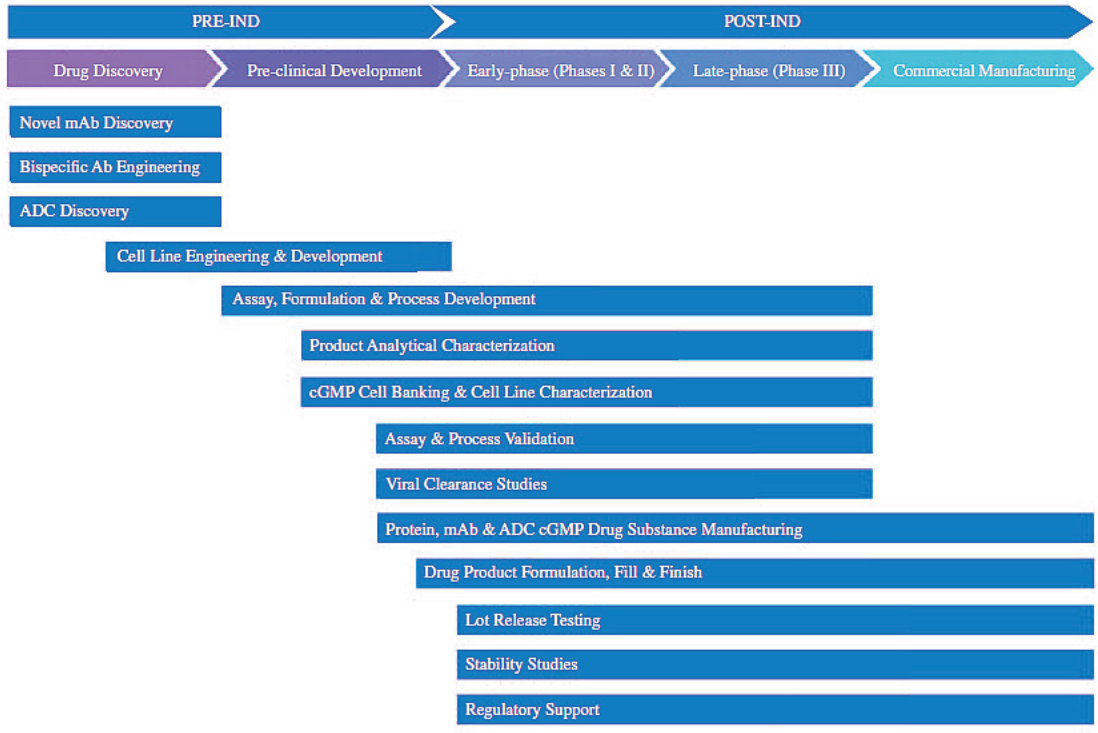
TABLES

CHAPTER 1: INTRODUCTION: BRIEF HISTORY OF CHINA BIOPHARMA SERVICE INDUSTRY

Service and Business Model of a Biologics CMO

Biologics (biopharmaceuticals) are a subset of pharmaceuticals and are revolutionizing the treatment of diseases in many major therapeutic areas globally, primarily benefiting from groundbreaking progress in genetics, molecular biology and biochemistry over the past three decades. The biologics development process typically spans five stages: (i) therapeutics discovery, (ii)pre-clinical development, (iii) early-phase (Phases I & II) clinical development, (iv) late-phase (Phase III) clinical development, and (v) commercial manufacturing. Services required for the biologics development process can be grouped into two categories: (1) pre-IND or pre-clinical trial services, which include services provided during the first two stages of the biologics development process, and (2) post-IND services, which include services provided during the remaining three stages of the biologics development process.

Fig 1: Services of a Biologics CMO[1]



Source: WuXi Biologics Prospectus

Business model of CDMOs

A CMO can utilize both a fee for service (FFS) or full-time equivalence (FTE) model to generate revenue.

- Under the FFS model, a CMO would determine the fee level for each discovery, development or manufacturing step based on the scope of the services required for achieving such step, the estimated costs and expenses of the required services, the amount of time allocated for achieving such discovery, development or manufacturing step, the desired profit margin, the prices charged by competitors for similar services, among others. Under the FFS service contracts, in addition to service fees, sometimes CDMOs leverage integrated biologics technology platforms and proprietary technologies to receive additional fees in the form of milestone and royalty fees. The milestone fee structure allows a CMO to receive, on top of the service fees, a milestone fee or reward (typically ranging from RMB 0.5 million to RMB 50 million, approx. $USD $70,000 to $700,000) for each preset development milestone reached. The milestones are typically a critical point in the biologic's development process, such as the signing of the service contract, the completion of an important discovery, start of trials, development of a manufacturing step, or the success of a regulatory filing. Royalty fee structures allow a CMO to receive, on top of the service fees, typically up to 8% of the sales revenue (net of taxes; usually much less) of the relevant biologics product for a period ranging between five years and 15 years, if such product is successfully commercialized.
- Under an FTE model, a customer requests a CMO to assign a team of scientists to its project at a fixed rate per FTE employee per period of time. Total amount of service fees is based on the number of scientists and the amount of time required for completing the project, among others. Plus, hybrids or combinations of these two approaches can be used.

Biologics CDMOs Have High Barrier for Entry in China

Providing services mostly for biopharmaceutical development and manufacturing, there are high barriers to enter the CMO industry in China. The barriers can be summarized in the following aspects:

a) High capital investment

Construction of a GMP/cGMP grade facility means a lot of capital investment, which can be as high as hundreds of millions of USD; the initial investment for a stainless-steel bioreactors-based facility is especially high.

b) Technical barriers

Biologics CDMOs are a technology intensive industry. Bioprocessing demands a lot of expertise and specialized equipment, especially in manufacturing, assay development, quality assurance, etc.

c) Talent barriers

It is difficult to recruit and retain a professional team specializing in bioprocessing in China. Most of the returnee scientists in biopharma have focused on R&D instead of bioprocessing.

d) Clients/reputation barriers

It takes time for China-based biologics CMO to build reputation in the industry and track record with clients. Chinese CDMOs overall have not earned a reputation for quality and attaining GMP comparable to most Western CDMOs. With all Chinese CDMOs being new, with CDMOs and providing biologics manufacturing services to other companies only became legal at the central government level in the past few years, Chinese CDMOs simply have not had a chance to develop a solid reputation.

e) Management barriers

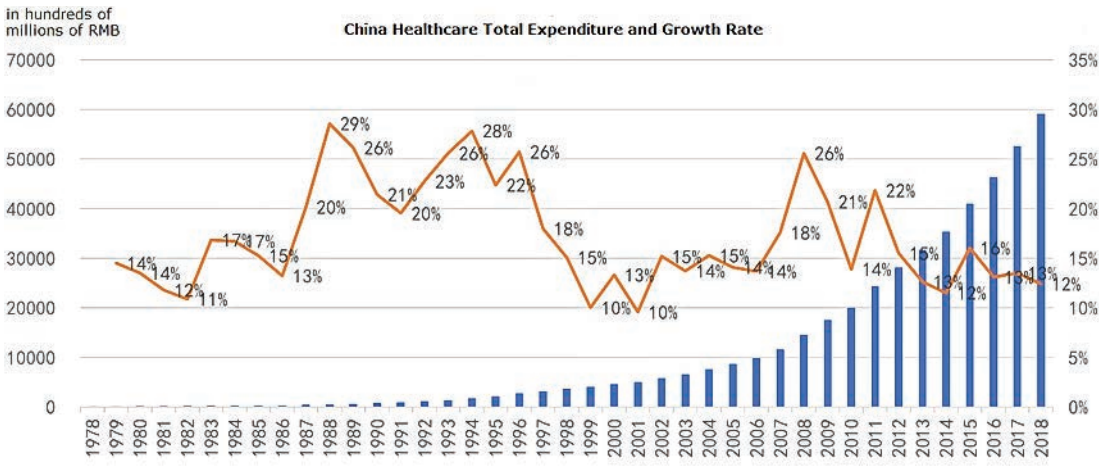
Biologics CDMOs need to establish reliable cost control, quality assurance and EHS management systems, which are quite complicated tasks for domestic companies.

As the biologics CDMOs mainly serve biotherapeutics development and there are high barriers for entry, it is a relatively young industry China which only comes into being recently.

Strong Growth Provides CMO Opportunities

The past decade has witnessed significant changes in China's biopharmaceutical landscape as China grows into world's second largest pharmaceutical market, driven by economic growth, urbanization, a population rapidly growing older as well as greater access to the national healthcare insurance program. According to health-care information company IQVIA, China was the world's second-largest national pharmaceutical market in 2017 with $122.6 billion revenue and also the biggest emerging market for pharmaceuticals with growth projected to reach $145 billion to $175 billion by 2022 as healthcare total expenditure keeps on growing at double digit rates annually[2]. Alongside robust growth of the pharmaceutical market as a whole, the structure of China's pharmaceutical consumption keeps on trending towards a greater market share of biological therapeutics, especially monoclonal antibody (mAb)s therapeutics, with a current wave of biosimilar/me-too mAb development by domestic developers as well as mAb therapeutics from multinational companies entering China.

Fig 2: China Healthcare Total Expenditures and Growth Rates[3]



Source: CINDA Securities Research Report: Analysis on 2019 China Healthcare Encyclopedia

China launched its first made-in-China mAb therapeutics only in 2005, and still has an underdeveloped market for biopharma therapeutics. The market penetration rate of biopharma therapeutics, and especially that of mAb biologicals, will increase in China as multiple sales statistics clearly show the domestic biopharmaceutical market growing at a higher rate than that of the broader pharmaceutical industry as a whole, with mAb therapeutics specifically growing faster than the biopharma market.

Biological therapeutics currently compose 25% -30% of the total global pharmaceutical market. China had a market share of 11.9% in 2015 and is projected to reach 18.6% in 2020[4]. China biologics markets have grown from under USD $10 billion in 2012 to a projected USD $50 billion in 2021 with a CAGR of 16%. In 2014, the market size of mAb therapeutics in China reached CNY 5.03 billion (USD $729 million). Some analysts expect that by 2020, the total China market for mAb therapeutics will reach CNY 28 billion[5] (USD $4 billion).

China is experiencing a second wave of biologics development, which is mAb therapeutics. In 1990s, there was a first wave of biological therapeutics development of insulin, EPO, TPO, interleukins, etc., simpler proteins which are produced from bacteria-based system and mostly just biogeneric copies of well-established Western products (a good place to start). But the bubble busted due to the small market size back then and too much homogeneous competition. Regulatory authorities in China gave dozens of BLAs to each such biogeneric during the period, but nowadays usually only a few developers are still making and selling them in a commercially relevant way[6]. In 2005, Citic Guojian (now part of 3S Guojian), launched the first 'made-in-China' mAb therapeutic, Yisaipu, which is a biogeneric version of Amgen's Enbrel (etanercept). Yisaipu quickly became a commercial success in China, generating over 1 billion RMB, (approx. USD $~140 million) in revenue in 2018[7] with a combined revenue in billions of RMB since its launch. This success lead to stronger developers' interest in mAb therapeutics and the 2nd wave of biologics development. Since 2011, over 100 companies have applied for INDs for their mAb projects[8], and quite a few domestic developers have launched their mAbs on the domestic and non/lesser-regulated international markets.

Table 1 mAbs from Domestic Developers Launched in China

Company Name	Project Name	Time of Launch	Revenue Information
Bio-Thera Solutions	Adamulimab biosimilar	Launched in 2019	NA
Shanghai Henlius Biotech	Herceptin (trastuzumab) biosimilar (HLX-02)	Launched in 2019	NA
Hisun Pharma	Humira (adalimumab) biosimilar	Launched in 2019	NA
Innovent Biologics	IBI-308, PD-1 mAb	Launched in 2019	USD $48 million in 2019 H19 (financial statement)
BeiGene	BGB, tislelizumab, a PD-1 mAb	Launched in Dec 2019	NA
Qilu Pharma	Avastin (bevacizumab) biosimilar (Qilu)	Launched in Dec 2019	NA
Shanghai Junshi Biosciences	JS-001, a PD-1 mAb	Launched in 2019	USD $44 million in the first half year of 2019[10]
Hisun Pharma	Enbrel (etanercept) biosimilar	Launched in 2015	USD $26 million in 2018[11]
Kanghong Pharma	Langmu (conbercept), a Lucentis biobetter	Launched in 2014	USD $126 million in 2018[12]
Celgen Shanghai	Enbrel (etanercept) biosimilar (Qiangke)	Launched in 2011	NA
BioTech Pharma Beijing	Taixinsheng (cancer mAb)	Launched in 2009	USD $23 million in 2009, increased significantly to USD $141 million in 2018 after getting into NRDL[13]
3S Guojian	Enbrel (etanercept) biosimilar (Yisaipu)	Launched in 2005	Over USD $140 million in 2018[14]

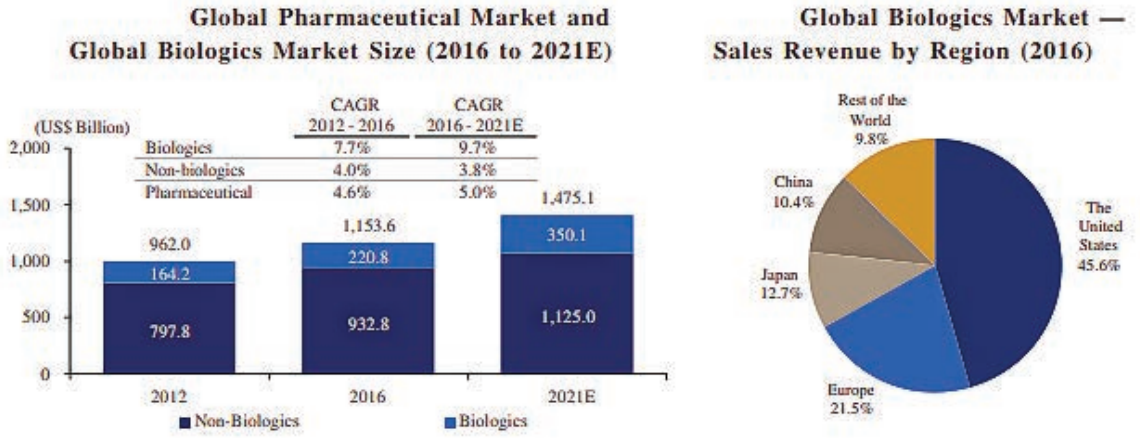
Source: BioPlan Associates Internal Study & NMPA

BioPlan's internal study also shows that over 300 mAb therapeutics are under clinical development in China, with CD20, HER2, EGFR, VEGF, TNF-alpha being the hottest targets. As development of this wave of mAb therapeutics development was initiated only around a decade ago with the majority of companies starting their mAb development within the recent 5 years or so, regulatory authorities in China have just started giving a green light to this wave of mAb projects. The year 2019 witnessed three PD-1 mAb therapeutics manufactured by domestic companies being approved, but the peak of mAbs development has certainly not arrived yet, as close to 20 PD-1 mAbs are currently under development by domestic companies[15]. Meanwhile new investments are still coming into this sector and hardly a month passes without news about companies being founded with a focus on mAb therapeutics.

Our research has shown a consensus among industry insiders that in the next 5 years China will see at least 10 mAb therapeutics from domestic companies getting Chinese BLA approvals, with the more optimistic projection at over 50 or so[16]. As more biological therapeutics are approved

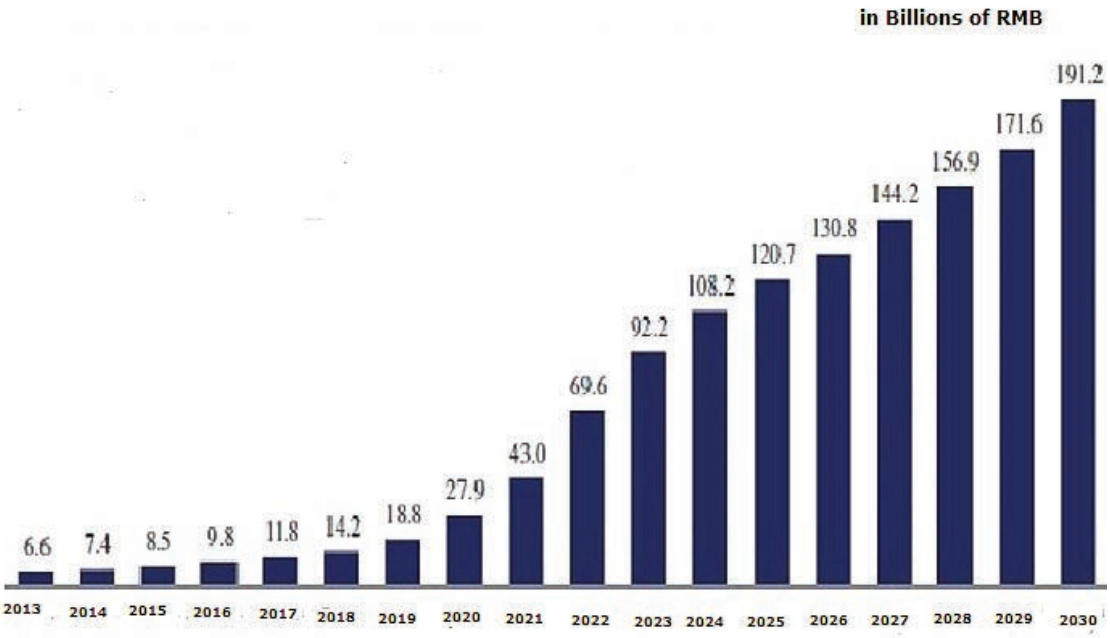
and enter the market, their penetration rate will certainly be on the rise. Currently, China only occupies ~10% of the global biologics market[1] while China's pharmaceutical market is 17.5% of the global drug market[17]. Analysts have reason to believe that China's biologics market share has potential to grow to a level that is similar to its share of the total pharmaceutical market.

Fig 3: Global Biologics Market[5]



Source: Advances in Biopharmaceutical Technology in China, Soc. Ind. Microbiology, and BioPlan Associates, Inc., (2nd Edition). 2018

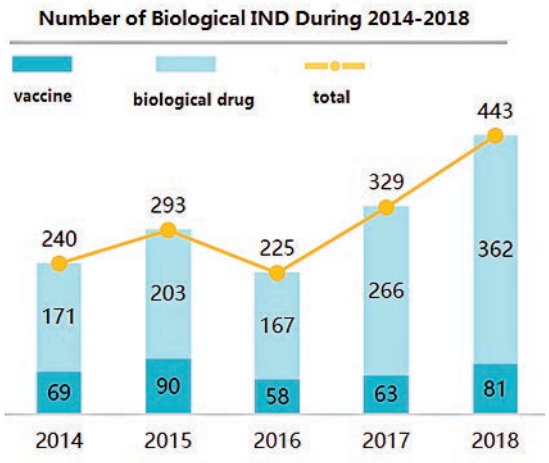
Fig 4: Market Size of mAb Therapeutics in China (2013-2030)[18]



Notes: Data projections after 2018 are:
CAGR between 2013-2017: 15.6%
CAGR between 2017-2022: 42.6%
CAGR between 2022-2030: 13.5%

Source: MabPharma Prospectus

Fig 5: Growth in Biological Therapeutics Projects in China 2014-2018[19]



Source: Dingxiangyuan Yizhuang Presentation 2019

The robust growth of the domestic biological therapeutics market, boosted by the national healthcare program, is likely to continue. The market size of biological therapeutics is largely dependent upon the expansion of the national healthcare program. While mAb therapeutics used to be regarded as 'luxury drugs' excluded from the National Reimbursement Drug List (NRDL; which establishes controlled prices for pharmaceuticals which can be reimbursed by the national healthcare insurance), recent years have seen more of them getting added into the NRDL. Altogether over a dozen mAbs are listed in NRDL including adalimumab, rituximab, Yisaipu (TNF-II receptor-antibody Fusion protein), golimumab, basiliximab, tocilizumab, bevacizumab, nimotuzumab, trastuzumab, omalizumab, sintilimab, cetuximab, ranibizumab, and conbercept[20]. Other biologics manufactured and marketed in China include insulin, interferon, TPO, EPO, interleukins, growth factors, urokinase, streptokinase, blood coagulation factor VIII, etc.

China has been updating the NRDL recently and each year regulatory authorities hold NRDL negotiations with pharmaceutical companies regarding agreed upon prices to get into the list. Getting into the NRDL would usually mean a rise in revenue, but at the cost of higher prices and profit margins.

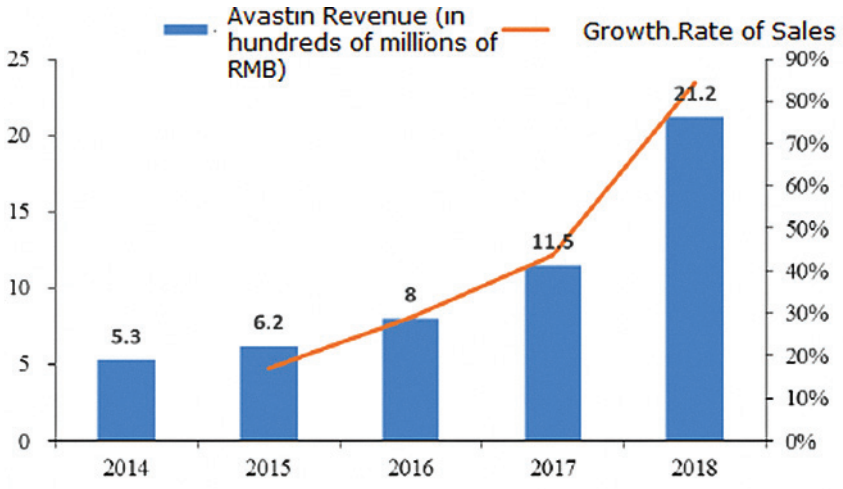
Table 2 Partial List of mAbs in NRDL and Price Reduction[21]

Name of mAb	Price before listed in NRDL (USD)	Price after listed in NRDL (USD)	Reduction Rate (%)
Rezumumab	1,400	814.3	42%
Trastuzumab	3,500	1,086	70%
Bevacizumab	714.3	285.7	60%
Nimotuzumab	514.3	242.9	54%
Cetuximab	605.7	185	70%
Rituximab	2,291.6	1,184	48%

Source: 2019 Industry Report on mAb Drug, Northeast Securities

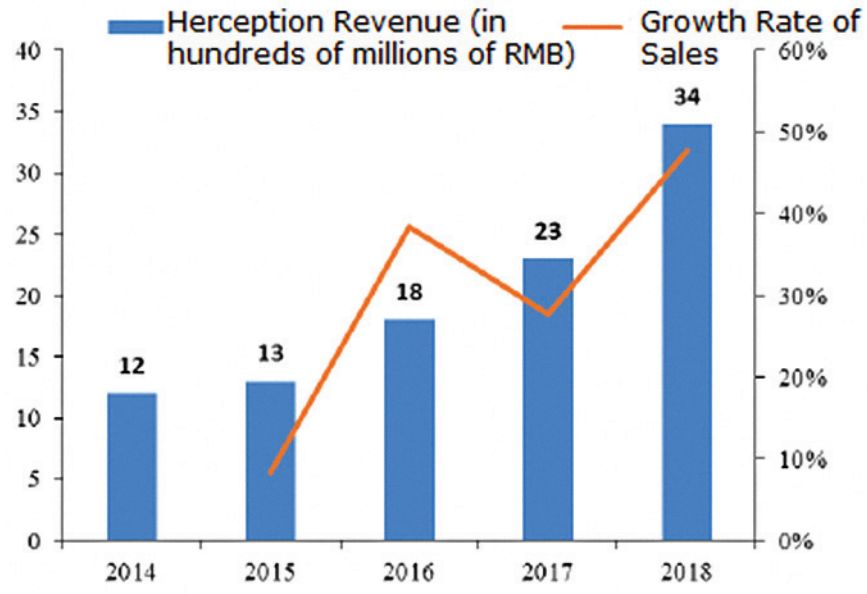
The price reductions are considered as squeezing the profit margin quite significantly by pharmaceutical companies. But for therapeutics that have already have a good reputation, the increase in revenue seems to well worth the price reduction, as we see in Herceptin and Avastin's cases. Both mAbs were listed in NDRL in 2017, followed by a jump in revenue in 2018.

Fig 6: Revenue and Growth Rate of Avastin Before/After Listing in NRDL[21]



Source: 2019 Industry Report on mAb Drug, Northeast Securities

Fig 7: Revenue and Growth Rate of Herceptin Before and After Listing in NRDL[21]



Source: 2019 Industry Report on mAb Drug, Northeast Securities

Meanwhile the Chinese government has made it clear that national healthcare insurance would adopt a policy of value-oriented strategic procurement. The strategy can be interpreted as the following:

1. The NRDL needs continuous updating (possibly annual updating) to eliminate the safe but non-effective pharmaceuticals and add new drugs with better efficacy (including the now expensive mAbs) which address unmet clinical needs.
2. The NRDL wants to procure these new pharmaceuticals with good efficacy at a discount price. The pharmaceuticals manufacturers can offset the price reduction with greater sales revenue and higher market shares.
3. The NRDL is also expected to encourage innovation in China's pharmaceuticals development by adding innovative drugs developed by domestic companies into the list. This can mean giving favorable policies to domestic innovators.
4. Costs of healthcare and expansion of NRDL will rise in phases without drastic growth.

The national healthcare insurance program is 1,760 billion RMB (USD $250 billion) in 2018, which is only ~2% of China's GDP but covers ~80% of China's 1.3 billion population, and it's expected to grow at a rate not significantly higher than the projected annual GDP growth rate (5%-6%) and healthcare costs could become a burden that erodes economic growth[22]. However, in recent years, China's healthcare costs and the national healthcare insurance have been growing at an annual rate significantly over 10% as they starts from a low baseline and there is strong demand from the Chinese public to have insurance reimburse more drugs, especially the newer, more expensive drugs (such as mAbs). For example, in 2018 the national healthcare insurance program has a total revenue of RMB 2,138 billion (approx. USD $313 billion), which is 19.3% higher than that in 2017 and comprises 2.4% of China's GDP in 2018[23]. There is also concern of over-drafting of the national healthcare insurance in recent years, and the government wants to limit annual growth of healthcare costs at ~10%.

The Chinese central government wants to adopt a policy of value-oriented strategic pharmaceutical procurement to fulfill its objective to control annual growth rate of healthcare costs at ~10%, which means de-listing of safe but ineffective pharmaceuticals and incorporating new pharmaceuticals with clear efficacy at a price discount. Usually when a new pharmaceutical gets listed into the National Reimbursement Drug List, its price would have to get reduced significantly. For example, when Innovent's PD-1 mAb went into NRDL, the price was cut by 64%[24]. In 2017, Ministry of Human Resources and Social Security organized negotiations on 45 patented drugs selected by experts committee; and 36 of them entered the NRDL as a result, with average price reduction of 44%[22]. The government's intention to control healthcare costs growth at around ~10% certainly means the NRDL will not expand drastically as has been expected. As the principle of strategic procurement is intended to benefit patients as well as bringing up a strong pharmaceutical industry in China, it is also well expected that the national healthcare insurance would play a pivotal role in encouraging innovation and R&D in China's biopharmaceutical industry by favoring relatively innovative domestic companies, such as Innovent. Though its PD-1 mAb is basically a fast follow-on biopharmaceutical, as a biobetter it is considered to be an innovative therapeutic by Chinese standards.

For Ordering Information on the Full Report

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