Building a World-Class Innovative

Therapeutic Biologics Industry in China

RDPAC

Bio

This report is written by China Association of Enterprises with Foreign Investment R&D-based Pharmaceutical Association Committee (RDPAC) in coordination with The Biotechnology Industry Organization (BIO) and the support of The Boston Consulting Group (BCG)

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Foreword

The bio-industry has been designated as one of China's seven strategic emerging industries (SEI) by the government. Within the bio-industry, therapeutic biologics[1] hold significant promise for China to achieve breakthrough innovation and to address largely unmet medical needs in many disease areas, including diabetes, cancer, hemophilia, and immunological impairment.

Today, China's therapeutic biologics industry stands at RMB 18 billion, representing less than 2 percent of the global total.[2] As China aims to develop this industry, many questions need to be answered. Are there lessons learned from the development of China's small molecule and early-generation biologics pharmaceutical industries, and if so, what are they? How quickly can China catch up with leading countries in terms of breakthrough innovation? Can China's large unmet medical needs be translated into a meaningful market that attracts talent and economic activity to serve Chinese patients' needs?

This report is written by The R&D-based Pharmaceutical Association Committee (RDPAC) in coordination with The Biotechnology Industry Organization (BIO) with the support of The Boston Consulting Group (BCG). We provide an industry perspective on these questions as China pursues innovation, industry competitiveness, and patient welfare in the development of the biotechnology sector.

About RDPAC: The R&D-based Pharmaceutical Association Committee (RDPAC) is a committee of the China Association of Enterprises with Foreign Investment (CAEFI). It is a non-profit organization made up of 37 member companies with pharmaceutical research and development capabilities. Among them, RDPAC members have 49 plants and 30 R&D centers, invested RMB 20 billion during the eleventh Five-Year Plan, and introduced 543 new molecular entities. Altogether, they manufacture and sell 2,817 different medicines. RDPAC's vision is to be a valued partner in delivering the "Healthy China 2020" goal of improving the health and quality of life of the people in China.

About BIO: The Biotechnology Industry Organization (BIO) is the world's largest biotechnology trade association. BIO is a non-profit organization headquartered in Washington, D.C. It represents more than 1,200 companies, universities, and research institutions that use biotechnology to research and develop cutting-edge healthcare, agricultural, industrial, and environmental products and applications. Currently, there are more than 400 biotechnology drugs in clinical trials targeting more than 200 diseases.

About BCG: The Boston Consulting Group (BCG) is a global management consulting firm and the world's leading advisor on business strategy. They partner with clients from the private, public, and not-for-profit sectors in all regions to identify their highest-value opportunities, address their most critical challenges, and transform their enterprises. Their customized approach combines deep insight into the dynamics of companies and markets with close collaboration at all levels of the client organization. This ensures that clients achieve sustainable competitive advantage, build more capable organizations, and secure lasting results. Founded in 1963, BCG is a private company with 78 offices in 43 countries

Executive Summary

Therapeutic biologics provide significant benefits to human health and address many unmet medical needs. While several developed countries have a clear lead in biologics, China has the potential to build a world-class innovative biologics sector if policies to support this ambition are well formulated and implemented in a timely manner.

With the increasing prevalence of diseases that are, and could be treated with biologics, China has a large potential demand for biologics. At the same time, China has a wealth of scientific resources and talent to drive future innovation. The task at hand is to harness the potential in both the scientific community and the marketplace to create the right conditions and incentives for breakthrough innovation and commercial success.

Benchmarking other countries, as well as examining China's small molecule pharmaceutical and early-generation biologics sectors show that policies should focus on both supply and demand. This creates industry players that invest in continuous innovation, produce high quality products, proactively build the market, and make better use of resources. These key success factors are particularly important as biologics have unique characteristics that make it incrementally challenging to manage innovation and ensure high quality production.

To achieve China's ambition of establishing a world-class innovative biologics industry, it is important to recognize the specific characteristics of biologics and tailor policies accordingly. We have developed several recommendations and outlined policy priorities that we believe will create a favorable environment and market conditions to nurture this unique industry.

Ensure medicines are safe and effective, with a reliable and efficient regulatory system

Ensuring the safety and efficacy of medicines requires collaboration between industry, government, and providers. While strict policies and regulations regarding the testing and evaluation of medicines can prevent poor quality, unsafe, or clinically ineffective medicines from reaching patients, these policies and regulations can also be barriers to bringing innovative new therapies to market. Therefore, an appropriate balance needs to be adopted to avoid stifling innovation. We see several opportunities to remove these barriers and create an environment where government and industry can effectively collaborate to accelerate access to new therapies, and ensure that poor, unsafe, or clinically ineffective medicines are kept out of the market by bringing China into alignment with international standards and best practices:

- Revise regulatory requirements to reduce time lag in introducing new medicines to China
- Reform the production licensing system to give innovators focus and reduce cost & complexity
- Clarify the definition of biologics and biosimilars and establish a clear biologics and biosimilars regulatory pathway with appropriate standards and requirements

Enable access for patients and reward innovation by creating a viable biologics market

China can become an even more commercially attractive market than it is today. Enhancing reimbursement and strengthening intellectual property (IP) protection will motivate leading biologics innovators to invest in the research & development (R&D) needed to develop their products for China, and also help build a strong domestic industry. We strongly recommend the following actions:

- Leverage diversified sources of funding to provide reimbursement to patients
  - Accelerate inclusion of innovative biologics on provincial and national reimbursement lists
  - Dedicate special government funding to reimburse innovative drugs
  - Encourage diversified funding sources including commercial insurance
- Provide robust IP protection for biologics by broadening patent scope and granting data exclusivity
  - Expand the scope of protection for molecule patents in examination practices
  - Provide data exclusivity to biologics

Cultivate new therapies and set the stage for innovation with the next generation of R&D talent and capabilities

China has been focusing on enhancing its R&D and manufacturing capabilities by providing funding, recruiting talent, and encouraging industry-academia collaboration. We suggest further developing and refining this, in particular, encouraging more global involvement and collaboration to enhance capabilities in translational medicine and establishing mechanisms to bring discoveries from research labs to the patient.

Many global innovative companies, large and small, which are involved in the bio-industry, would like to support the Chinese government in building a world class biologics industry in China. There are five areas in which innovative global companies could add significant value:

- Bring innovative products to patients in China and educate medical professionals
- Participate in industry development through investment and collaboration
- Incubate talent for local industry development
- Cooperate with Chinese companies entering the global market
- Bring in expertise from other countries to support Chinese policy making

Global innovative companies already conduct these activities in China today, and they can continue to augment their degree of investment and participation beyond current levels.

1

The Importance of the Therapeutic Biologics Industry

Value to patients

Therapeutic biologics are changing patient lives by addressing significant unmet medical needs for many critical diseases. From recombinant human insulin to interferons to monoclonal antibodies (mAb), biologics have saved patients' lives and improved quality of life for patients suffering from diabetes, infectious diseases, hemophilia, and cancer. For other debilitating diseases, therapeutic biologics are the best and in many cases, the only available disease-modifying drugs for patients.

Value to industry

Therapeutic biologics are an important component of, and are expected to be a key growth driver for the global pharmaceutical industry. In 2010, biologics already accounted for approximately 17 percent of the total global pharmaceutical market.[3] Ten out of the top 30 pharmaceuticals (in terms of revenue) are biologics.[3] They have gained significant share in key therapy areas: in 2010, the biologics industry accounted for 79 percent of global immunology sales and 35 percent of oncology sales.[3] It is estimated that from 2011 to 2016, the global biologics industry will grow at approximately 7 percent annually, outperforming the estimated 3 percent annual growth of the rest of pharmaceutical industry.[3]

Value to the economy

According to the government's 12th five-year plan for bio-industry in China, therapeutic biologics, along with other biotech products in the fields of agriculture and energy, constitute the broader bio-industry[4] that is expected to grow as fast as 20 percent annually[5] and reach approximately US$630 billion[6] in 2015. With the right enabling policies, the broader bio-industry could become one of China's pillar industries by 2020. As one of the most advanced technology-intensive industries, the bio-industry will help China transform from a labor-intensive economy to a knowledge-intensive economy and contribute to the sustainability of future economic growth.

While several developed countries have a clear lead in biologics, China has the potential to build a world-class innovative biologics sector

China's therapeutic biologics market is still emerging, accounting for only 2 percent of the value of the global therapeutic biologics market, while the overall Chinese pharmaceutical market accounts for 7 percent of the global market.[2,3] In recent years, there has been a shift in the global drug market from small molecule drugs to biologics, with biologic share increasing from 13 percent in 2006 to 17 percent in 2010.[3] However, in China, the percentage of biologics has stayed flat at around 5 percent for the past five years.[2]

The global biologics industry, which was established only three decades ago, has a much shorter history than the small molecule industry. Although China is a latecomer to the biologics industry, it can leverage the existing innovation and capabilities in developed countries and learn from their successes and failures. Since the industry is still nascent, China has the opportunity to shape the direction of development, establish high standards, stimulate innovation, and bring benefits to patients.

China has a large potential demand for biologics

China has large and growing unmet medical needs. With a fast aging society, rapidly changing lifestyles, and environmental pollution, the incidence of many diseases has grown significantly. For example, new cancer cases in China have increased from 2.2 million in 2002[7] to 2.8 million in 2008[8,9] and are expected to further increase to 3.9 million in 2020.[8,9] Diabetes prevalence among adults has increased from 2.5 percent in 1994 to 9.7 percent in 2008.[10] For these diseases, biologics can provide successful treatments, ensuring that the demand for biologics will continue to grow.

China has a large potential talent pool to tap into to drive continuous innovation, which would address unmet medical needs for Chinese patients

The biologics industry is driven by strong life sciences talent and China has put significant emphasis on developing its talent pool and attracting experts from abroad. Local universities and institutes produce a large number of undergraduates in life sciences each year, establishing a solid foundation for the biologics industry's talent pyramid. Key biotech labs across the country train technical and R&D staff. There are also a large number of foreign-based top-tier scientists of Chinese origin who are interested in returning to China. According to the Ministry of Science and Technology (MOST), 30 to 40 percent of global peer-reviewed publications involving biotech are written by people of Chinese origin.

In order to fully tap into the potential of Chinese talent and the country's latent demand, China needs to build a better R&D infrastructure, provide sufficient training, and offer incentives to attract, develop, and enable this talent pool.

2

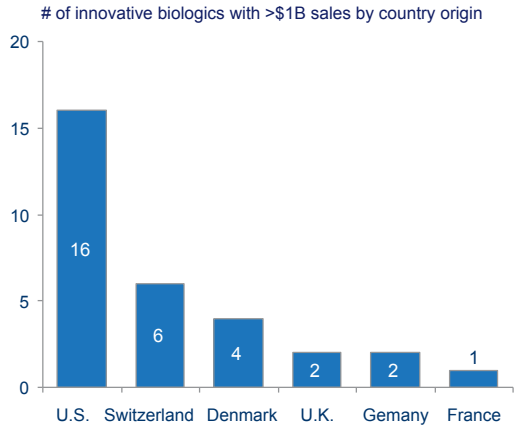
Key Success Factors in Developing the Therapeutic Biologics Industry

2.1 Learning from global experiences: Comparative studies of policy impact on the development of the therapeutic biologics industry

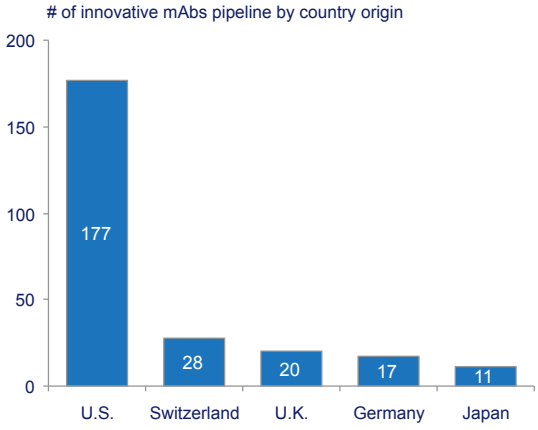
Globally, most innovative biologics have originated in the U.S. and Europe, followed distantly by Japan. Other benchmarked countries still lag behind in breakthrough innovation (Exhibit 1).

Exhibit 1. Most innovative marketed and pipeline biologic products originate in the U.S. and Europe

All 31 top biologics with sales over $1B in 2010 were originated from the U.S. and Europe



Innovative biologics pipeline (mAbs as an example) is also concentrated in U.S. & Europe



Source: IMS; Top 50 Biologics, Contract Pharma 2011; Datamonitor; BCG analysis

We reviewed government policies from the U.S., Europe (using the U.K. as an example), and Japan to illustrate how government action has shaped the industry landscape and set the stage for success. We also selected several other Asian countries that are actively developing biologics industries to understand how they are pursuing their ambitions.

Several learnings emerged from the comparative study:

Lesson 1. Both demand-side and supply-side policies are needed to cultivate the biologics industry

The U.S. is both the largest biologics market and the leading country in biologics innovation. The success of the U.S. biologics industry can be attributed to many factors including strong industry investment, but government policy has been a key factor. The government established the goal of building an innovation-driven bio-economy and has used both pull and push policy levers to create an attractive market environment and cultivate innovation.

The U.S. provides strong IP protection with data exclusivity, a streamlined regulatory timeline, and broad market access. The country has a mature patent law and litigation system and recently adopted a 12-year data exclusivity period for biologics.[11] Despite a stringent regulatory review and approval process, including clinical trial requirements, the U.S. Food and Drug Administration (FDA) has been efficient and supportive by delivering timely and specific guidance and predictable approval timelines to applicants. Market pricing and broad reimbursement coverage are also provided to innovative biologics. Commercial insurance is highly developed, accounting for one third of U.S. healthcare spending. Government programs also provide reimbursement for some patients, covering most biologics.

The U.S. government provides the largest funding for life sciences R&D globally and has attracted top talent from around the world. Small biotech firms receive funding through special programs and tax credits are offered at the federal and state government levels to incentivize innovation. The U.S. also has a well-developed venture capital market, investing the largest amount globally (close to US$4 billion) each year on biotech companies[12], with a significant portion to early-stage companies. Not surprisingly, the U.S. is home to the world's largest biotech clusters. These clusters house the largest number of top-tier life sciences research universities and centers in the world, as well as the largest number of start-ups in which basic research findings are further developed into new medicines. Universities, research institutes, biotech companies, and VCs are in close proximity and are well-coordinated with each other, so that the creation and expansion of innovative biotech start-ups are accelerated.

The U.K. has also created favorable market conditions for innovation and market demand. For example, the U.K., like other EU countries, has strong IP protection, with 11 years of data exclusivity, universal healthcare coverage, and efficient regulatory processes. The government is now focusing more on supply-side levers by providing investment and incentives for biologics R&D, especially early-stage biotech firms, and cultivating innovation in several biotech clusters across the country.

Due to these attractive market environments, major pharmaceutical companies have been investing in biologics in the U.S. and Europe for years. In turn, these companies have contributed immensely to the development of the local biologics industry.

Lesson 2. Without effective policies in place to convert demand into commercially viable supply, demand alone cannot drive the development of the biologics industry

Japan has a strong life sciences base and a favorable market environment but proper policies have not been established to stimulate the commercialization of biotechnology research, which has led to slower development of the biologics industry than in the U.S. or Europe.

Japan has a relatively large domestic market in which most innovative biologics are reimbursed. There are also efficient regulatory processes in place as well as good IP protection. However, external sourcing of innovation is limited in Japan. Strategic alliances are uncommon and large companies still rely on in-house development.[13] In addition, there is a lack of mobility for first-rate scientists and skilled workers from internal R&D organizations and universities to start-ups.[14] Lastly, financial resources to back highly risky investment projects are still lacking: R&D spending by Japanese biotech companies is still low compared to the U.S.[14]

Recognizing these issues, the Japanese government has named this century the "life sciences century" and aims to strengthen its industry's development by implementing a set of policies that will incentivize the commercialization of innovation from academic institutions to the marketplace.

Lesson 3. Even with a relatively small domestic market, demand in the global market and strong supply-side policies can drive industry development

Singapore has devoted significant resources and enacted numerous policies to develop the local biologics industry. Singapore applied strong supply-side policy levers by devoting capital and talent to discovering breakthrough innovation in biologics (and pharmaceuticals in general). Generous financial incentives helped attract first-rate scientists and engineers in life sciences from around the world. Due to these efforts, the number of researchers and scientists in the biomedical industry increased from zero before 2000 to 2,962 in 2006;[15] most of which are foreigners. Major tax incentive programs have also attracted global companies such as Lonza and Genentech, which have set up two of the world's largest biologics manufacturing facilities in Singapore. Between 2000 and 2010, biomedical industry manufacturing output rose from US$5 billion to US$18 billion.[16] With a limited local population, attracting foreign talent and investment is indeed an effective approach to boost industry development. While there is no question that Singapore has made considerable progress as a manufacturing center, whether Singapore can become an innovative hub remains to be seen.

India has a limited biologics domestic market due to minimal affordability and access. By 2010, only approximately 25 percent of the population was covered by some form of health insurance.[17] However, even with health insurance, reimbursement for innovative biologics has remained low. In addition, poor IP protection exacerbates the unattractiveness of the Indian biologics market, which has led to limited foreign and domestic investment and low levels of collaboration in the biologics industry. As China aims to build an innovative biologics industry, we need to learn from the situation in India and create a favorable market and regulatory environment to cultivate the industry. With the limited local opportunities, Indian companies such as Cipla and Dr. Reddy are looking for success in the global biologics market based on

their achievements in the small molecule generics business. With a small domestic market, the global market is the clearest route to success. However, achieving success in the global market may be challenging due to differences in quality standards.

Korea has made a number of investments to support the local biologics industry. Although the government intended to cultivate original innovation, local players have mainly focused on biosimilars and the market environment is still quite restricted with very low prices and narrow reimbursement guidelines. There is an open question as to whether Korea can successfully transition from biosimilars to innovative biologics. Although their base in biosimilars capabilities can provide a strong technical foundation due to overlap in production methods and processes, there are many aspects of the innovative R&D market that will not develop without focused attention.

2.2 Learning from local experiences: A retrospective view of the development of the Chinese small molecule pharmaceutical industry and early-generation biologics industry

Lesson 1. Appropriate quality standards are needed to avoid overcapacity and ensure quality

In the small molecule pharmaceutical industry, low regulatory standards have resulted in the creation of thousands of generics manufacturers in China. Companies compete on price and some resort to cutting corners on quality in order to win. The most recent scandal involving a large and previously reputable business for its use of industrial-grade gelatin in capsule raw material reminds us that quality and patient safety continue to be issues in the industry. As industry players are able to satisfy China's Good Manufacturing Practice (GMP) requirements without aligning with global standards, there is little incentive for companies to meet global standards, without which it would not be possible to access global markets. As an official from the Ministry of Industry and Information Technology (MIIT) acknowledged, the Chinese government recognizes these issues in the small molecule industry and is now working diligently to enhance the global competitiveness of the industry through a series of policy levers.

In the case of large molecules, the quality of some local erythropoietin (EPO) products, which is a biologic drug primarily used to treat anemia by stimulating red blood cell production, remains an issue. A study in 2009 comparing the quality of EPO products from Asian producers with the originator showed that EPO from some small local Chinese companies displayed quality discrepancies and contained different glyco-forms and impurities.[18] Even batches from the same company had product quality differences. Low quality EPO can have immunogenicity issues, leading to the formation of neutralizing antibodies and thereby compromising endogenous EPO. As a result pure red cell aplasia (PRCA), a severe consequence, can develop.[19]

Historical lessons can be drawn, that high regulatory standards are required to only allow high-quality players to enter the market.

Lesson 2. Mechanisms to reward innovation are critical to incentivize the right industry behavior

Lack of strong IP protection and financial reward in the small molecule pharmaceutical industry has resulted in low R&D investment in China. With the exception of a few leading companies, the industry spent on average just 4% of revenue on the development of drugs. Given their generic portfolios, companies also have not invested in market building activities such as physician and patient education on diseases and treatments. In fact, most companies outsource sales and distribution to distributors and do not have direct contact with end-customers (physicians and hospitals).

The early-generation protein biologics sector, which includes medicines such as EPO, has a history similar to that of the small molecule industry. Local EPO was first launched in the Chinese market in the late 1990s and a total of 16 local manufacturers received an EPO license. Due to heavy competition, the price for local EPO (2,000 IU) dropped 90 percent within three years, from over US$20 prior to 1998 to approximately US$2 in 2001. The low price of EPO led to lower profitability and Chinese EPO players were unable to invest in innovative R&D. 3S Bio, a first-mover on aggressive pricing, achieved market leadership with approximately 40 percent share of the EPO market.[2] Only recently has 3S Bio achieved higher profitability and started to increase R&D investment.[20] It is still unclear how this market's growth and evolution will impact innovation.

Recognizing the lessons learned from the small molecule industry, the government has put in place several policies. First, there has been substantially more stringent enforcement of and continuous improvement on GMP standards. Second, the differential pricing policy given to first-to-market and differentiated generics allows companies to receive up to a 30% price premium. This effectively rewards companies who have achieved incremental innovation. We already observe leading players responding to the policy by shifting their portfolio, attracting talent for innovation and focusing on manufacturing quality. However, how these policies will drive behavior in the biologics sector remains to be seen. In the following chapter, we will explore further the current state of development and challenges for the therapeutic biologics industry.

3

Current State of Development and Key Challenges of China's Therapeutic Biologics Industry

China has made a significant commitment to the development of the broader bio-industry and recognizes therapeutic biologics as a key pillar. We see three key areas where current policies are creating challenges for patients and innovators: regulatory policy and processes, market access mechanisms, and support for innovation:

1. China's regulatory framework, approval processes, and enforcement present barriers to ensuring safe and effective medicines are available to patients in a timely manner
- Regulatory challenges have led to a significant lag in bringing new medicines to China
- China's production licensing system, in particular the lack of a market authorization holder (MAH) system, limits supply chain flexibility and efficiency and stifle innovation
- Regulatory pathway and standards for biosimilars are not clear

2. Patients' access to biologic therapies is limited by reimbursement policies and relatively weak IP protection
- Current reimbursement policies are inhibiting the use of biologics and limiting the incentive for innovation
- Challenges of IP protection and lack of alignment with global standards creates uncertainty for innovators

3. China has a good basis for innovation, but further effort is needed to focus investments and stimulate the next generation of talent and medicines
- The Chinese government is very active in attracting talent to China, but more can be done to fill gaps in breadth and depth of experience
- Government spending on life sciences R&D is increasing, while private funding has not been a mainstream funding source in China
- Broad collaboration between industry, academia, and the medical community has started but is still limited

Below, we explore each of these ideas in greater detail, providing specific examples and a frank assessment of the current landscape in China. In chapter 4, we offer our thoughts on potential solutions and our recommendations to create a self-reinforcing ecosystem that benefits both patients and innovators.

3.1 China's regulatory framework, approval processes, and enforcement present barriers to ensuring safe and effective medicines are available to patients in a timely manner

Ensuring the safety and efficacy of medicines requires collaboration between industry, government, and providers. While strict policies and regulations regarding the testing and evaluation of medicines can prevent poor quality, unsafe, or clinically ineffective medicines from reaching patients, these policies and regulations can also be barriers to bringing innovative new therapies

to market if they are poorly or improperly designed or if their potential implications have not been fully assessed. While a highly conservative approach can appear to be the safest, an appropriate balance is needed to avoid delaying life-saving medicines and stifling innovation. In today's regulatory environment, we see several areas where policies or the lack thereof, are barriers rather than enablers:

3.1.1 Regulatory challenges have led to a significant lag in bringing new medicines to China

Most new biologic drugs experience a 5 year lag from the first international NDA approval to Chinese regulatory approval, though it is theoretically possible to shorten this to ~1.5 years with global simultaneous development. This "drug lag" means that years pass with Chinese patients not having access to the latest therapies that are available in many other countries around the world. While there are many reasons for this lag, we would like to highlight three areas that are major barriers: long CTA timelines, restrictions on global simultaneous development, and specific challenging regulatory requirements.

It takes an average of 19 to 22 months for therapeutic biologic drugs to receive CTA approval in China[21], whereas the process for small molecule drugs typically takes 10–18 months.[22] Two critical drivers of this delay are the lack of reviewer resources and technical know-how within the State Food & Drug Administration (SFDA) and Center for Drug Evaluation (CDE), and the biological sample test requirements necessary for a clinical trial at the National Institutes for Food and Drug Control (NIFDC). In the U.S. and South Korea, clinical trial applications can be approved in as little time as 30 days, by conducting review processes more quickly, and/or exempting certain testing requirements if the appropriate conditions are met.

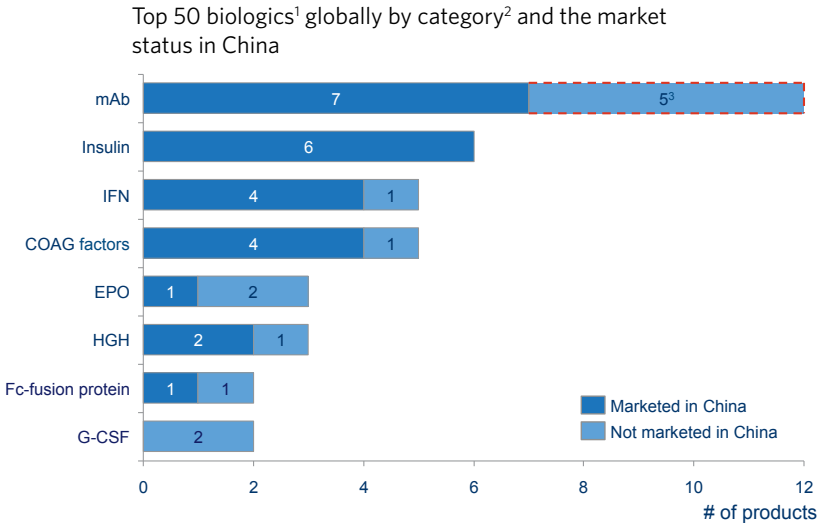
With global simultaneous development, new medicines undergo clinical testing in parallel with other countries, including the U.S. Current regulations and regulatory policies create barriers for companies attempting to include China in global Phase 3 trials, and very substantial hurdles for companies seeking to conduct early stage clinical trials including First-in-Human (FIH), Phase 1 and 2 trials.

Furthermore, there are several specific requirements of the drug registration process that unnecessarily contribute to the complexity of registering new medicines in China. One key barrier is clinical sample size requirements. There is currently a "one size fits all" minimum patient sample size requirement for biologics, rather than basing sample sizes on scientific requirements and taking into account the full package of global data. A second barrier is in China's CMC requirements. These requirements create additional hurdles and are not aligned with global standard practices. This includes the level of detail and data required during the CTA application process, the lack of a mechanism to allow for CMC changes once the CTA is approved, and the difficulty

in implementing post-marketing approval changes. In contrast, the U.S. and EU permit changes in the manufacturing process as long as the comparability is assessed according to the ICH Q5E international standards. A third barrier is the requirement that the reference country Certificate of Pharmaceutical Product (CPP) must be issued prior to NDA application (when using regulatory pathways based on reference country CPP). Many countries permit NDA applications prior to CPP issuance, but hold NDA approval until the CPP is approved. As the current NDA review time is 15–18 months, this requirement significantly increases the lag in approval versus other international markets.

These hurdles raise barriers to the registration new biologics, inhibit biologics innovator's motivations to innovate and delay the China launch of new drugs, resulting in postponed patient access to new biologics therapies. As a result of these hurdles, many latest innovative biologics are not yet in the China market (see Exhibit 2).

Exhibit 2. Some top innovative biologics are not yet available to Chinese patients



1. Top 50 in 2010 by global revenue 2. Some categories including vaccines are not included 3. Tysabri, Synagis, Xolair, Soliris and Actemra
Note: mAb: monoclonal antibody; IFN: interferon; COAG factors: coagulation factors; EPO: erythropoietin; HGF: human growth factor; G-CSF: granulocyte colony-stimulating factor
Source: Top 50 Biologics, Contract Pharma, 2011; SFDA; BCG analysis

3.1.2 China's production licensing system, in particular the lack of a market authorization holder (MAH) system, limits supply chain flexibility and efficiency

China's regulatory system currently requires combined management of marketing authorization and production authorization. This scheme creates a significant challenge, since manufacturing in China cannot easily be conducted in production facilities not owned by the innovative company. Unlike other major countries, China lacks a MAH system, which allows a pharmaceutical company to hold the marketing license without having their own production facilities. This system is common practice globally, including in the U.S., Europe, Japan and South Korea.

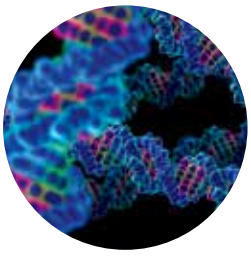
Under an MAH system, innovators can develop their supply chain in the most efficient and effective manner, including using third-party facilities, while still being ultimately responsible and accountable for meeting the regulatory requirements for manufacturing. In the absence of such as system, innovators may be forced to build duplicative facilities, diverting resources and focus that could be devoted to researching and developing the next generation of medicines.

3.1.3 Regulatory pathway and standards for biosimilars are not clear

China's current regulatory framework does not require non-innovative biologics to prove equivalence in efficacy, quality, and safety through systematic comparison with the originator. Instead, it allows non-innovative biologics to be registered as new biologics products but with less stringent requirements. However, these practices may pose a risk to patients as poor quality biologics have the potential to induce undesirable immune responses, which can reduce efficacy or even cause harm to patients. These effects have been demonstrated in several studies[23] and in particular, a recent study[23] in Thailand found that use of a recombinant human EPO induced neutralizing antibodies and 23 out of 30 patients developed pure red-cell aplasia, a condition requiring life-long red blood cell transfusions.

All biologics in China are classified in categories 1 through 15, depending on their marketing status and product types. Although categories 1 through 12 are technically required to conduct clinical trial Phases 1, 2, and 3, the SFDA has the flexibility and discretion to require administrative additions or exemptions for preclinical tests and clinical trials. Thus, abbreviated regulatory processes or lower standards without proof of equivalence could be adopted. For biologics in categories 13 through 15, requirements are even less stringent, with only clinical trial Phase 3 being required. Because of the unique characteristics of biologic products, non-innovative biologics cannot be assumed to have the same properties as innovative products. Therefore, in the absence of a comprehensive biosimilarity assessment, non-innovative biologics should go through the same rigorous testing as the innovative product. An abbreviated regulatory process with lower standards poses significant risks on product safety and efficacy. This regulation framework is inconsistent with global norms and can expose patients to unknown risk. Furthermore, with such local standards, it is challenging for locally registered products to gain access to foreign markets and compete globally.

China is now considering developing a biosimilars pathway. A clear biosimilars pathway aligned with global standards (e.g. the WHO Guidelines on Evaluation of Similar Biotherapeutic Products) will help address the risks in the current system. Pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of therapeutic biologics can be affected by slight alterations in the production process. Thus, while comparative analytical studies of molecular characteristics and quality form the foundation of the biosimilarity assessment, appropriate non-clinical and clinical studies are needed to ensure the safety and efficacy of the biosimilar product. Analytical characterization and quality assessments should be followed by preclinical and clinical testing to establish that neither identified *nor* undetected quality differences are clinically meaningful. Global innovative companies, and increasingly top Chinese biologics companies, are advocating for such a biosimilars pathway with higher quality standards.



With China's increasing use of biologics and biosimilars, attention and focus on post-marketing surveillance is of continued importance. While many regulations are in place, there is limited enforcement. Local manufacturers rarely file adverse drug reaction (ADR) reports and there are rarely penalties imposed on manufacturers who fail to report. In China, most ADR reports are from medical institutions, while approximately 14 percent of ADR reports filed in 2011 were from manufacturers and marketers.[24] This can be compared to the U.S., where 90-plus percent of ADR reports are from manufacturers.[25] Additionally, since the onset and incident rate of possible adverse events can be unpredictable, long-term post-marketing surveillance is critical for patient safety. Ongoing monitoring and surveillance post-marketing can help to identify rare safety signals, such as immunogenicity, in a large population. It is important to ensure

appropriate and enforced post-marketing surveillance when biosimilars are used. If non-innovative biologics are used interchangeably with each other or with originator products, the adverse effects associated with low quality biological products will be difficult if not impossible to track.

3.2 Patient access to biologic therapies is limited by reimbursement policies and relatively weak IP protection

In addition to ensuring the safety and efficacy of biologic medicines, government policy should also enable market access and drive market demand. This includes providing mechanisms for the reimbursement and funding of biologics, as well as IP protection. These policies will allow patients to access the benefits of new therapies and reward innovators. We see two critical demand-side barriers in the current policy environment:

3.2.1 Current reimbursement policies are inhibiting the use of biologics and limiting the incentive for innovation

Reimbursement for advanced biologics is currently very limited. The government is the dominant reimbursement source for China's health care system and there are no mAb products currently on the National Reimbursement Drug List (NRDL). A few mAbs are listed on some of the Provincial Reimbursement Drug Lists (PRDL), but these are mainly for in-patient treatment and require high out-of-pocket co-payments.

NRDL listing opportunities open every four to five years. Yet even if biologics are listed, usage is constrained by the reimbursement expense cap and reimbursable indications. The hospital expense caps for reimbursement are especially unfavorable for expensive innovative biologics and the reimbursable indications are often narrower than the labeled indications. Tendering processes can also add additional delays in speed to market. For drugs that are listed on the NRDL or PRDL, tendering at the provincial level can take one to three years while the actual hospital listing can take an additional one to three years.

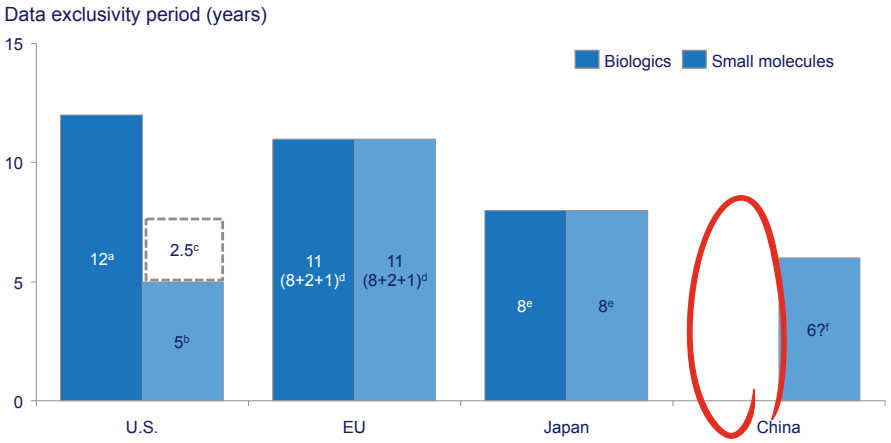
As a result, Chinese adoption rates for innovative therapeutic biologics are extremely low. In the case of rheumatoid arthritis (RA), approximately 1–2% percent of urban eligible Chinese patients receive biologic DMARD (Disease-Modifying Anti-Rheumatic Drug) treatments.[26] In contrast, the biologic DMARD treatment rate for RA patients in Germany is 8%, U.K. is 10%, and Spain is 17%.

3.2.2 IP protection challenges and the lack of alignment with global standards creates uncertainties for innovators

The unique characteristics of biologic molecules make it challenging to adequately protect such products using biologics patents. China's current patent protection environment is less than desirable for innovators as the scope of patent protection is narrower than global standards. To be patentable, a biologic molecule patent claim is typically a specific sequence or a series of sequences. Therefore, a biosimilars manufacturer can change the protein sequence slightly to create a molecule that avoids incurring infringement liability, a situation that is avoided elsewhere by recognizing that biologic molecules that have only minimal conservative substitutions in the sequence cannot be patented by non-innovator firms. However in China for example, three similar molecule patents from different biologics manufacturers co-exist for Rituximab, which was originally developed by Biogen Idec/Roche.[27] Both global innovative companies and Chinese biologics companies have expressed concerns over what is perceived to be a weaker patent protection environment than global standards.

Due to the difficulty of protecting innovation through molecule patents, data exclusivity protection is even more critical for biologics. It is an important process to ensure adequate returns to innovators for a fixed time period. However, China does not clearly grant data exclusivity protection for biologics. While New Drug Registration has set data exclusivity at six years for new chemical entities,[28] it is unclear whether this includes biologics and, if so, whether it can be effectively enforced. All major innovation-driven countries allow data exclusivity for biologics that is similar in length or longer than the time-frame allowed for small molecules.[29] For example, the U.S. grants 12 years for biologics compared with five years for small molecules (see Exhibit 3).

Exhibit 3. Data exclusivity is allowed in many other countries, but not clearly granted in China for biologics



a. No biosimilar application until 4 years after reference product approval; no biosimilar approval until 12 years after reference product approval; b. No generic application until 5 years after originator product approval (early as 4 years with patent challenge); 3 additional years for new indications, which is not linked to the initial 5 year period; c. 30 month stay of approval in the event of a patent challenge ; d. For products submitted for approval after 2005, no biosimilar / generic application until 8 years after reference / originator product approval; no biosimilar / generic approval until 10 years; 1 year additional for significant new indications approved during first 8 of the 10-year period; e. Eight-year period of post-marketing surveillance during which no generic or biosimilar application may be approved; f. Six-year data exclusivity is granted for new chemical entities in Drug Registration Regulation but its application is unclear for either small molecules or biologics
Source: Literature review; BCG analysis

3.3 China has a good basis for innovation, but further effort is needed to focus investments and stimulate the next generation of R&D talent and medicines

While China has a large potential talent pool to drive continuous innovation, there is more that can be done to build better R&D infrastructure, provide sufficient training and offer good incentives to attract, develop and enable this talent pool.

3.3.1 The Chinese government is very active in attracting talent to China, but more can be done to fill gaps in breadth and depth of experience

The Chinese government has put in significant effort to attract global talent by initiating programs such as the Thousand Talent Plan. However, China still lacks scientists with drug discovery and process development experience, since many of them prefer to stay overseas.

3.3.2 Government spending on life sciences R&D is increasing, while private funding has not been a mainstream funding source in China

The Chinese government's total annual spending on R&D (estimated to be US$25 billion in 2010) is not far behind other developed countries (U.S. spending estimated to be over US$100 billion[30], German spending estimated to be US$28 billion[31]). However, the Chinese government's annual expenditure on life sciences R&D still lags behind other developed countries.[32] In addition to government funding, more diversified funding sources for innovation need to be encouraged (e.g., private funding). However, private funding in China for biotech and breakthrough innovation is still very limited.

3.3.3 Broad collaboration between industry, academia, and the medical community has started but is still limited

Across industry, academia, and the medical community, stakeholders are driven by different motivations. For example, academics generally focus on generating high quality research results to be published in academic journals, while industry players need tangible drug concepts with clear commercial value and feasibility. Unlike in the U.S. or Europe, the process to commercialize academic discoveries is not well established in China. There is weak precedence of venture capital funding, or experienced technology transfer teams in academic institutions. While a translational medicine institute has recently been created within the Chinese Academy of Sciences, and some top universities such as TsingHua have its own fund for commercializing university research, much more is needed to establish mechanisms to bring discoveries from research labs to the patient.

4

Building a World-Class Innovative Therapeutic Biologics Industry

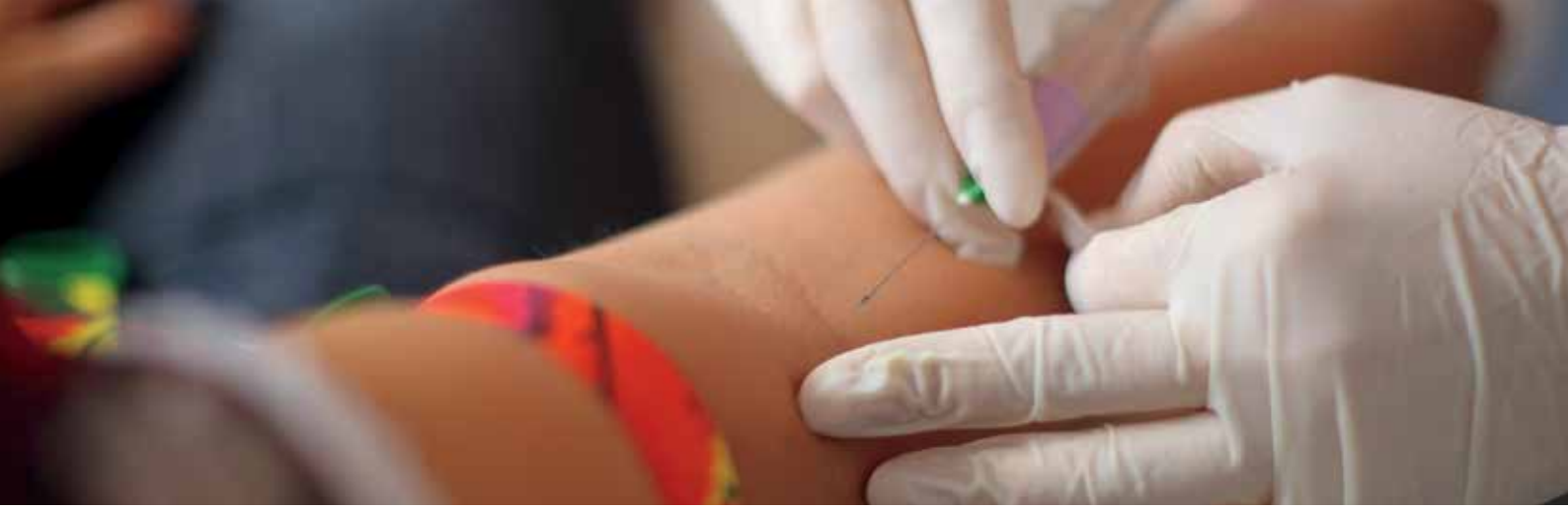
China has traditionally focused on supply levers supporting scientific discoveries to address unmet patient needs. These levers include talent recruitment and government funding in R&D. These efforts will continue and be strengthened, as indicated in multiple government policies highlighting the strategic importance of the biologics sector. On the demand side, more needs to be done to create an attractive market for therapeutic biologics in China. Only with an attractive market will the private sector be willing to increase investment into this sector. By establishing and maintaining balance between both supply and demand, the growth of the biologics sector can be accelerated and sustainable to reach a global leadership position.

To achieve the ambition of building a world-class biologics industry, we believe there should be greater emphasis on demand-side levers, while simultaneously retooling supply levers. Our policy recommendations are summarized below. These policies can incentivize the following desired industry behaviors: investing in R&D to continuously innovate; choosing to produce high quality products that are closer to global standards; and actively educating and building the market to improve patient health. To achieve this, we believe reform and further investments are needed in three areas:

1. Ensure medicines are safe and effective, with a reliable and efficient regulatory system
- Revise regulatory requirements to reduce time lag in introducing new medicines to China
- Reform the production licensing system to give innovators focus and reduce cost & complexity
- Clarify the definition of biologics and biosimilars and establish a clear biologics and biosimilars regulatory pathway with appropriate standards and requirements

2. Enable access for patients and reward innovation by creating a viable biologics market
- Leverage diversified sources of funding to provide reimbursement to patients
- Provide robust IP protection for biologics by broadening patient scope and granting data exclusivity

3. Cultivate new therapies and set the stage for innovation with the next generation of R&D talent and capabilities
- Encourage more collaboration among industry, academia, and the medical community
- Encourage more global collaboration



The detailed recommendations are outlined below:

4.1 Ensure medicines are safe and effective, with a reliable and efficient regulatory system

As described above, we see several areas where current regulatory policies are barriers to making safe and effective medicines available to Chinese patients in a timely manner. Here, we present our recommendations for removing these barriers and creating an environment where government and industry can effectively collaborate to accelerate access to new therapies, and ensure that poor, unsafe, or clinically ineffective medicines are kept out of the market. These recommendations would bring China closer in alignment with international standards and best practices:

4.1.1 Revise regulatory requirements to reduce time lag in introducing new medicines to China

First, we recommend streamlining regulatory procedures and requirements, in alignment with global standards, to accelerate CTA application review and approval of new medicines. Accelerating the clinical trial review process will have multiple benefits. It will reduce China's new drug approval time lag, and increase opportunities for Chinese patients to participate in global Phase 3 trials, while maintaining high quality data on safety and efficacy. As an example, Japan has made substantial investments in building talent and in streamlining clinical and marketing approval processes. This has dramatically reduced the drug introduction timeframe and allowed Japanese patients to benefit more quickly from innovative medicines.

Second, we recommend removing barriers to global simultaneous development. Companies should be encouraged to include China in global Phase 3 trials, and also to conduct earlier stage clinical trials (FIH/Phase 1/Phase 2) in China. By more tightly integrating China into global development plans and strategies, innovative companies can quickly and efficiently generate the high quality, scientifically sound data required to demonstrate safety and efficacy. This will reduce drug lag and increase Chinese patients' access to potentially life-saving drugs.

Third, to align with global practices and encourage testing of innovative biologics in China, we recommend key changes to the regulations on local clinical sample size requirements, CMC, and CPP requirement at NDA application. We recommend that China study patient sample size requirements incorporate the full global data set available and be based on scientific needs rather than strict minimums. This will allow an efficient and robust approach to generating the relevant clinical data that are needed to ensure the safety and efficacy of medicines for Chinese patients. On CMC, we recommend aligning with global standards on the data requirements at CTA application, creating a mechanism to allow changes after CTAs have been approved, and adopting a streamlined approach to allow appropriate, well-managed process and

manufacturing site changes after marketing approval is received. For NDA applications, we recommend allowing innovators to file NDA applications prior to the issuance of a reference country CPP. SFDA would then process the application but not approve the NDA until the reference country CPP is received and reviewed.

Taken together, these recommendations would bring China's regulatory frameworks and processes in line with well-accepted global practices. Removing these barriers will stimulate innovator activities in China and reduce drug lag without any compromise to patient safety as well prepare Chinese companies to participate in the global market.

4.1.2 Reform the production licensing system to give innovators focus and reduce cost & complexity

Biologics manufacturing facilities are a substantial investment and require a high level of expertise to operate reliably and efficiently. We recommend establishing a MAH system in China, which allows a pharmaceutical company to hold the marketing license and manufacture their product in China without owning their production facilities, while still being ultimately responsible and accountable for meeting the regulatory requirements for manufacturing. This allows appropriate legal control and accountability while providing the innovator with critical flexibility to efficiently manufacture their medicines.

To support the establishment of a MAH system, we also recommend allowing biologics R&D companies to collaborate with experienced international-standard contract manufacturing companies for the production of biologics. This will allow innovators to focus on R&D activities that are their key competencies. Contract manufacturing for biologics could be piloted on a limited scale in certain provinces first with leading and qualified global CMO players. After the benefits and safety have been proven and the relevant regulatory authorities have gained experience in managing CMOs and contractors, it could be rolled out more broadly. Ultimately, this can improve the standards of local manufacturers and enhance China biomanufacturers' global competitiveness.

4.1.3 Clarify the definition of biologics and biosimilars and establish a clear biologics and biosimilars regulatory pathway with appropriate standards and requirements

Many companies are currently developing and marketing non-innovative biologics, however as described above, the regulatory framework and requirements for biosimilars are unclear and inconsistent with evolving global standards. We recommend clarifying the definition of biologics and biosimilars, and establishing a clear pathway for biosimilars with the standards and requirements needed to ensure patients receive safe and effective medicines. The first step in this process would be to evaluate and reconsider the current categorization scheme for biologics. Subsequently, appropriate requirements should be established regarding how biosimilarity, safety and efficacy of biosimilars will be assessed. This should include circumstances under which clinical trials should be required and when alternative supporting data can be used. We strongly recommend that these guidelines be established in a timely manner and aligned with the global principles that have been adopted by the EU and WHO. The specifics of such guidelines and policy are beyond the scope of this report, but RDPAC stands ready to discuss this topic in greater detail.

In addition, we believe that post-marketing surveillance can be better implemented in the China market to ensure the safety and efficacy of biologics. To supervise mandatory reporting of ADR from manufacturers and marketers, detailed guidelines on when and what to report as well as how to respond to reports should be implemented. Special attention should be paid

to immunogenic events and evaluation studies should be used to assess the potential risk. For example, in the U.S., after identifying a safety concern in the adverse event reporting system, further assessment using other large databases is performed to decide if the regulatory body will take any action. In addition, penalties for manufacturer and marketer failure to report should be increased and reporting from patients and healthcare providers can be encouraged with new incentive mechanisms. Furthermore, drug safety and post-marketing surveillance regulations should conform to international standards and best practices, such as the ICH guidelines. Finally, it is considered best practice to have post-marketing studies tailored to the risk and benefit profile of the product. A robust pharmacovigilence plan should have adequate mechanisms in place to differentiate between the adverse events associated with the biosimilar product and those associated with the reference product. We suggest that China consider this practice going forward. While strengthening post-market surveillance is required, it should be acknowledged that it cannot replace the critical need for a clear and appropriate pre-marketing regulatory assessment.

4.1.4 Strengthen the overall regulatory environment

In addition to the specific recommendations above, we believe that the overall regulatory environment needs to be further strengthened for the benefit of the industry and patients. While detailed recommendations are beyond the scope of this report, there are key areas to highlight. The SFDA has faced an exponential increase in workload, both in volume and complexity. To help the SFDA, and in particular the CDE, keep pace, a substantial investment in resources, talent, and capabilities are needed. Beyond the SFDA, the infrastructure for clinical research should also be assessed and strengthened. The clinical trial site network, local Ethics Committees, and other elements required for safe and successful research should be reinforced to support the growing demands. Much attention is needed to ensure a healthy innovation environment.

4.2 Enable access for patients and reward innovation by creating a viable biologics market

While an efficient and effective regulatory system is critical to ensure medicines are available to patients, we believe it is also vital to address the demand-side barriers of reimbursement and IP protection. With proper reimbursement and strong IP protection, patients will be able to benefit from the medical advances of biologics, and innovators can be appropriately rewarded for their investments and risks incurred. Our recommendations are:

4.2.1 Leverage diversified sources of funding to provide reimbursement to patients

Today, the high burden of out-of-pocket costs limits many patients' access to innovative biologic therapies. To support biologics reimbursement, we recommend adopting diversified and creative approaches to funding innovative biologics:

Accelerate inclusion of innovative biologics on provincial and national reimbursement lists — Prioritizing important biologics that can treat critical diseases and including these drugs on the NRDL and PRDLs can help address the many urgent unmet medical needs of Chinese patients. Recognizing regional diversity, provinces that are more economically developed and have larger goals to stimulate the innovation industry can be encouraged to include advanced biologics on their PRDL. One possibility to address complexity would be to create a new category in the NRDL (e.g. "C" list in addition to the current "A" and "B") that covers biologics and advanced therapeutics. Establishing a new biologics-specific set of guidelines such as reimbursement levels and coverage requirements would avoid inadvertently disrupting the reimbursement structures and processes currently in place.

Dedicate special government funding to reimburse innovative drugs — China has one of the biggest economies in the world, but is still evolving in many respects. Compared to other major economies, healthcare spending as a percent of GDP is still very low at less than 5 percent.[33] Assuming that the Chinese biologics market grows at approximately 30% CAGR, it will reach US$10 billion by 2015 but still only account for less than 0.1 percent of total nominal GDP.[34] While reimbursing biologics would add to the government's financial burden, it provides significant value and impact to patient lives. Furthermore, this burden would be compensated manyfold through a thriving innovation sector. Some municipalities are taking the initiative and experimenting with dedicating resources to critical illnesses requiring biologics—one example is the recent reimbursement pilot in Qingdao. A special fund (US$47 million annually) was established to support reimbursement for critical illnesses as a complement to the basic medical insurance. Its focus is on supporting special drugs, including two biologics, Betaferon® and Herceptin®, and other large expenditures. These funds could be linked directly to the biologics-specific reimbursement list described above, allowing provincial or local governments the ability to customize resource levels and deployment.

Encourage diversified funding sources including commercial insurance — Globally, commercial insurance is an important mechanism that helps ensure patients have affordable access to innovative medicines. However, in China the huge potential of commercial insurance has yet to be explored. A tiered reimbursement system could allow the government to focus on basic healthcare needs and broad coverage, while commercial insurance could act as an important complement to address certain high-cost healthcare expenditures (e.g., biologic drugs, severe diseases). Progress has been made through the Critical Illness Insurance scheme released in August 2012, which outlines the government's plan to allocate part of the basic medical insurance fund to purchase Critical Illness Insurance from commercial insurance companies. If appropriate risk pools can be established, certain patient segments in China could gain access to, and would greatly benefit from privately purchased commercial insurance.

4.2.2 Provide robust IP protection for biologics by broadening patent scope and granting data exclusivity

Innovative medicines represent a substantial and high-risk investment, requiring commitment and significant resources over many years. Effective IP protection ensures that innovators are appropriately rewarded for making these investments. For biologics specifically, there are key gaps in China's current IP framework and enforcement system that should be addressed. We have two specific recommendations:

Expand the scope of protection for molecule patents in examination practices — to ensure that innovation is protected, we recommend expanding molecule patent claims to cover proteins or nucleic acid sequences including a reasonable degree of variation. In particular, innovative molecules should be protected against minor changes to amino acid sequence in non-functional parts of the molecule that do not disrupt the 3D structure or function. During the examination process, extra caution is needed to avoid granting two or more patents for what are essentially the same molecules.

Provide data exclusivity to biologic drugs. A major gap in the current IP framework is that China does not clearly grant data exclusivity protection for biologics. We recommend implementing a reasonable period of data exclusivity for biologics, consistent with all other drugs and in line with global standards. This protection will become even more important with the establishment of a biosimilars pathway. Utilization of non-clinical and clinical data is a significant advantage to companies who have not borne the commercial risk or invested

in the research required to bring a biologic to market. An appropriate period of exclusivity is required to ensure that innovators are both incentivized and rewarded by allowing them a reasonable opportunity to recoup their investment.

Overall, we believe a holistic approach will be the most successful in creating the conditions that foster innovation. Beyond clarifying the scope of patents and ensuring appropriate data protection, strengthening IP enforcement, including trademarks, and aligning practices with global standards (e.g., on new biological material deposits) will help reward true innovation. With the right IP environment, global and local innovators will find their efforts are rewarded and will be motivated to continue to make the investments and commitments needed to bring the next generation of medicines to Chinese patients.

4.3 Cultivate new therapies and set the stage for innovation with the next generation of R&D talent and capabilities

As described above, there have been substantial efforts to increase the quality and depth of the R&D talent pool, and also provide direct support to research institutions and key domestically-driven R&D projects that show high potential. We believe that these efforts should be continued, with even greater resources put behind them.

Beyond the current policy focus areas, we believe that strong emphasis should be placed on supporting and encouraging collaborations. While there is a growing trend of global collaboration in academia and industry (as evidenced by the numerous cross-border academic publications in leading journals, and R&D collaborations between global innovative companies and local companies), collaborations across different stakeholder groups are more limited. This area has traditionally been overlooked, even globally, although most major pharmaceutical companies are now actively engaging with leading academic institutions to collaborate on translational research. Building stronger translational medicine capabilities in China will help better translate research investments into marketed therapies and benefit Chinese patients. On this note, we recommend focusing on following two types of collaboration:

4.3.1 Encourage more collaboration among industry, academia, and the medical community

Industry players should be the core of such collaborations. University/research institutions can provide ample sources of ideas and innovation while the medical community can be an important contributor of practical experience and feedback. Establishing concrete mechanisms and incentives for communication and collaboration are also keys to success. For example, U.S. university/research institutions tend to have well-established systems and specialized teams to help researchers commercialize valuable research results.

4.3.2 Encourage more global collaboration

Providing attractive terms and conditions to global biologics companies would encourage them to establish R&D and manufacturing bases in China, which in turn will bring expertise and talent into China. The policy being piloted in Nanjing is an excellent example of how the government is already pursuing this.[35] Collaborations between global innovative companies and local companies could also be explored. One good example of this is the recent joint venture between MedImmune and WuXi AppTec, the first innovative biologics collaboration in China. Lastly, support could be provided for local companies to "go out" and collaborate with global innovative companies abroad to leverage global resources and capabilities outside China.

4.4 Practical and impactful immediate next steps

Recognizing that building a world-class biologics industry is a journey and not a sprint we have also prioritized three practical and impactful next steps to be considered in the nearer-term:

Drive demand through more diversified reimbursement schemes — Pilot diversified reimbursement schemes for biologic therapies in select provinces. We recommend conducting these pilots in a range of geographies with varying levels of resources and infrastructure to understand how approaches would need to be customized for broader rollout.

Reduce timeline and hurdles of innovative drug approval and market access — Regulatory policies should be aligned with international standards, especially speeding up CTA approval, creating an MAH system, and establishing a clear pathway for biosimilars. RDPAC is ready to establish an open communication channel with the SFDA to work together and ensure that patients have access to innovative new medicines.

Encourage global collaboration to accelerate industry capability and standards — Building upon existing efforts such as the Harvard-Fudan translational medicine collaboration, China can take the global partnerships to a new level by systematically building a network of partnerships among global innovative companies, local players, academia, and the medical community locally and abroad. The goal is to bring in global experience to help build a healthy ecosystem.

5

Global Innovative Companies as a Solution Partner

Global innovative companies are ready and willing to support the Chinese government in building a world-class biologics industry in China. There are five major areas in which these companies can add value:

- Bring innovative products to China and educate the market
- Participate in industry development through investment and collaboration
- Incubate talent for local industry development
- Help Chinese companies enter the global market
- Bring in expertise from other countries to support Chinese policy making

5.1 Global innovative companies are committed to bringing innovative and high-quality biologics drugs to China and to educating the market

Global innovative companies have raised patient treatment standards by investing heavily in high-quality innovative biologics and new therapeutic classes with significant results. The results of global company innovation, for example drugs such as Avastin®, Velcade® and Humira®, have provided significant value to patients around the world, and have substantially advanced global pharmaceutical industry innovation. China has also benefited from global company innovation. RDPAC members, for example, have introduced 42 biologics molecules into the Chinese market as of 2010, representing approximately 40 percent of all biologics sales in China.[2]

Meanwhile, global innovative companies have also made significant investments in educating local physicians on how to use innovative biologics safely and effectively. With the appropriate knowledge and resources, the local medical community can in turn educate patients on the potential benefits of advanced biologics and offer them innovative treatment options.

5.2 Global innovative companies are actively participating in the Chinese biologics industry through investment and collaboration

Global innovative companies have demonstrated their long-term commitment to innovation in China by directly investing in Chinese R&D centers. For example, the number of RDPAC member R&D centers in China has more than quadrupled over the last decade, from seven to 30, providing high-quality employment opportunities for scientists and clinicians in China.[22] More types of biologics R&D activities are also being established in China. Roche's footprint is an example: in 2004, Roche established an R&D center in Shanghai, China, the company's first R&D center in a developing market. In 2007, Roche upgraded the Shanghai R&D center to a full-function drug development center spanning the entire clinical development process, including drug design, clinical trials, and new drug registration. This center was the first of its kind in the Asia-Pacific region, and has brought significant global knowledge and expertise into China and helped China cultivate talent along the value chain.

Global innovative companies partner extensively with local research institutions, universities, hospitals, and biologics companies to support innovation in China. These partnerships cover a wide range of activities- from joint development projects to the transfer of key assets to local partners- and promote a vibrant and innovative R&D environment in China. For example, Novo Nordisk collaborated with the China Academy of Science in 2007 to set up a special research fund for biologics and diabetes-related research. Sanofi established a strategic partnership with the China Academy of Science-Shanghai Institutes for Biological Science in 2008, focused on developing new drugs in diabetes and oncology, and establishing a talent exchange program.

Global innovative companies are incubating local innovation in China through venture investment. By bringing their experience and funding to China, global innovative companies are helping incubate local innovation. For example, Eli Lilly set up Lilly Asia Ventures in 2007 to make venture capital investments in the life sciences and healthcare sectors. Lilly's investments in Asia, particularly in China, have helped establish role models and educate the local biologics investment community. In addition to Lilly, Merck has also partnered with the Shanghai municipal government's innovation fund to invest in a Chinese pharmaceutical start-up.

Global innovative companies are investing in biologics manufacturing in China. As these global companies establish manufacturing operations in China, they bring in expertise and develop local talent, ultimately helping China build capabilities in biologics manufacturing. For example, Novo Nordisk invested over US$400 million to build an insulin manufacturing site in Tianjin. This is the largest investment project for Novo Nordisk outside of Denmark, its home market and is expected to become its primary supply base in the Asia-Pacific market. As a leading global CMO for biologics, Boehringer Ingelheim (BI) is already working with Chinese biotech startups in cell-line and process development in BI's facilities in Europe. It is also actively developing opportunities to invest in a facility to offer high quality CMO services in China, which will help Chinese companies commercialize their biologic products at a faster pace.

5.3 Global innovative companies are developing and incubating talent through investment and operations in China

Global innovative companies provide a cutting-edge work environment for Chinese employees by providing industry and international exposure as well as top training opportunities across the value chain (R&D, commercial and operations) to local talent in the Chinese biologics industry. In turn, this talent base will be the future backbone in many local companies in China.

Many global company alumni are now helping various local biologics companies grow rapidly, from R&D firms like BeiGene to Contract Research Organizations (CROs) like Wuxi Apptec. Global companies are also a magnet for overseas returnees, many with extensive industry experience, who can further enhance the capabilities and global integration of China's biologics industry. Additionally, global innovative companies contribute to external talent cultivation across the value chain through various collaborations with local research institutions and industry players.

5.4 Global innovative companies can help Chinese companies enter the global market

China has a clear goal of cultivating domestic biologics players for the global playing field, and some local biologics players have already begun to enter the global market. The global reach and know-how of global innovative companies can help the Chinese biologics industry raise standards. It also makes global companies valuable partners for Chinese players with global ambitions. For example, Pfizer has entered into a joint venture with Hisun, not only to develop business in China, but also to help Hisun expand into global markets. Merck has a similar joint venture with Nanjing Simcere. We expect these collaborations to increase over time as more Chinese companies prepare for global entry.

5.5 Global innovative companies can help bring in expertise and experience from other countries to support the Chinese government in policy making

As leading global players, global innovative companies have extensive experience across different areas like IP, regulation, health economics, and reimbursement schemes in different global markets. By acting as solution partners to the government, these companies can share their know-how, knowledge and first-hand experience. This can help China learn, avoid unnecessary failures and setbacks, and build a healthier innovative ecosystem, ultimately accelerating the development of the biologics industry in China.

Summary

Therapeutic biologics is a strategically important industry for China. The Chinese government has set a high ambition for it to be an innovation-driven industry rather than a follower of innovations from other countries. However there are many hurdles to achieving the ambition. Industry regulatory policy and framework requires significant improvements if China desires to make the market more attractive to investment from local and global innovators. We have reviewed key regulatory reforms, demand-side and supply-side policies which we recommend exploring and implementing.

There are also important historical lessons to be learned from China's experience with the small molecule and early-generation biologics industries, as well as biologics industry best practices from around the world that China should consider.

The industry is still in the early stage of development. We believe that if China can set the stage for success as described in this report, a healthy ecosystem will develop- with active global player participation, thriving local industry and patients benefiting from the latest innovative therapies. China has the required elements for success, and should move aggressively to position itself as a global leader in the innovative therapeutic biologics industry.

Acronyms

ADR	Adverse Drug Reaction
BCG	The Boston Consulting Group
BIO	The Biotechnology Industry Organization
CAEFI	China Association of Enterprises with Foreign Investment
CAGR	Compound Annual Growth Rate
CDE	Center for Drug Evaluation
CMC	Chemistry, Manufacturing, and Controls
CMO	Contract Manufacturing Organization
CPP	Certificate of Pharmaceutical Product
CRO	Contract Research Organization
CTA	Clinical Trial Application
EPO	Erythropoietin
FDA	US Food and Drug Administration
GMP	Good Manufacturing Practice
IP	Intellectual Property
mAb	Monoclonal Antibody
MAH	Market Authorization Holder
MIIT	Ministry of Industry and Information Technology
MOST	Ministry of Science and Technology
NCE	New Chemical Entity
NDA	New Drug Application
NIFDC	National Institutes for Food and Drug Control
NRDL	National Reimbursement Drug List
PRDL	Provincial Reimbursement Drug Lists
RA	Rheumatoid Arthritis
R&D	Research & Development
RDPAC	The R&D-based Pharmaceutical Association Committee
SEI	Strategic Emerging Industries
SFDA	State Food and Drug Administration
SIPO	State Intellectual Property Office

References and Notes

1 Therapeutic biologics: a substance that is produced by or extracted from a biological source and intended for therapeutic purposes, often using recombinant DNA technology. Examples are, recombinant proteins, monoclonal antibodies, and advanced therapy medicinal products. Therapeutic biologics here exclude vaccines.

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Our Vision

RDPAC's Vision

Healthier China Through Innovation

To be a valued partner in delivering the "Healthy China 2020" goal to improve the health and quality of life of China's citizens and patients:

- Bring our high-quality and innovative healthcare products and services in a socially responsible and commercially viable manner;
- Committed to securing patients timely access to innovative & high quality drugs
- Achieve high standard of integrity for ethical research and business practice.
- Contributing to the growth of the biopharmaceutical sector in China;
- Supporting the development of a sustainable healthcare system in China

BIO's Vision

BIO's vision is to use its global experience to help China integrate its biopharmaceutical industry into global markets in a manner that promotes innovation and is aligned with international standards and practices.

RDPAC Member Companies

Abbott
Allergan
Astellas
AstraZeneca
Baxter
Bayer HealthCare
Biogen Idec
Boehringer Ingelheim
Bristol Myers Squibb
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Merck Serono
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