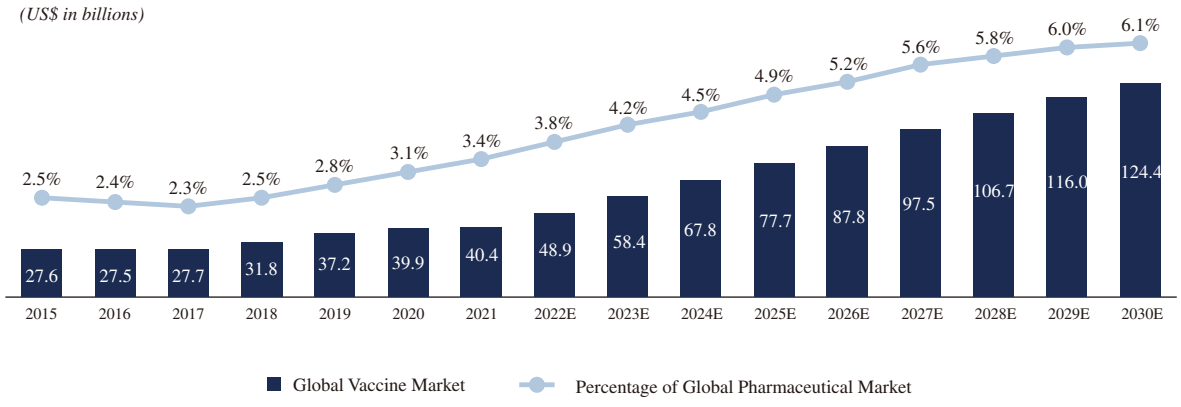
The information and statistics set out in this section and other sections of this document were extracted from the Frost & Sullivan Report, which was commissioned by us, and from various official government publications and other publicly available publications. We engaged Frost & Sullivan to prepare the Frost & Sullivan Report, an independent industry report, in connection with the [**REDACTED**]. *The information from official government sources has not been independently verified by us, the Sponsor or* [**REDACTED**], *and no representation is given as to its accuracy.*

OVERVIEW OF THE GLOBAL VACCINE MARKET

Vaccines are biological preparations that provide active acquired immunity against a particular disease. A vaccine typically contains one or several antigens from, or similar to, a disease-causing microorganism and improves immunity to a particular disease upon administration by inducing specific immune responses. Since the development of the first vaccine in 1798 to protect against smallpox, advances in biotechnology have promoted the development of vaccines. In the past two decades, the application of molecular genetics has furthered our understanding of immunology, microbiology and genomics, and their integration in vaccine research, which has led to the launch of innovative vaccines. The global vaccine market increased from US$27.6 billion in 2015 to US$40.4 billion in 2021 at a CAGR of 6.6%, and is expected to grow to US$77.7 billion in 2025 at a CAGR of 17.8% from 2021 to 2025, and further grow to US$124.4 billion in 2030 at a CAGR of 9.9% from 2025 to 2030. The chart below illustrates the historical and forecasted global vaccine market size for the periods indicated:

Global Vaccine Market, 2015-2030E

Period	CAGR
2015-2021	6.6%
2021-2025E	17.8%
2025E-2030E	9.9%



Notes:

(1) The assumption of the global vaccine market size is based on the increasing proportion of vaccines in the global pharmaceutical market, as well as the revenue data disclosed by the major vaccine manufacturers. The COVID-19 vaccine market is not taken into consideration.

(2) Percentage of global pharmaceutical market is calculated and forecasted based on 2020 data.

Source: Public disclosure of listed companies, expert interviews, Frost & Sullivan Analysis

The following table summarizes details of the top ten bestselling vaccines globally in 2021.

Ranking	Name of Vaccine	Manufacturer	Sales Revenue in 2021 (US$ billion)	Category
1	**Comirnaty**	Pfizer/BioNTech	Pfizer 36.78, BioNTech 3.56	Covid-19 mRNA vaccine
2	**Spikevax**	Moderna	17.68	Covid-19 mRNA vaccine
3	**Gardasil, Gardasil 9**	MSD	5.67	HPV vaccine
4	**Prevnar 13**	Pfizer	5.27	Pneumonia
5	**Vaxzevria**	AstraZeneca	3.98	Adenovirus-vectored Vaccines for COVID-19
6	**Flu vaccine (Fluzone, Flublok)**	Sanofi	3.11	Influenza
7	**Polio/Pertussis/Hib Vaccines**	Sanofi	2.55	Polio, Pertussis, and Hib Infection and etc.
8	**Ad26.COV2.S**	J&J	2.39	Adenovirus-vectored Vaccines for COVID-19
9	**Shingrix®**	GSK	2.37	Shingles
10	**ProQuad/M-M-R II/Varivax**	MSD	2.14	Measles, Mumps, Rubella and Varicella

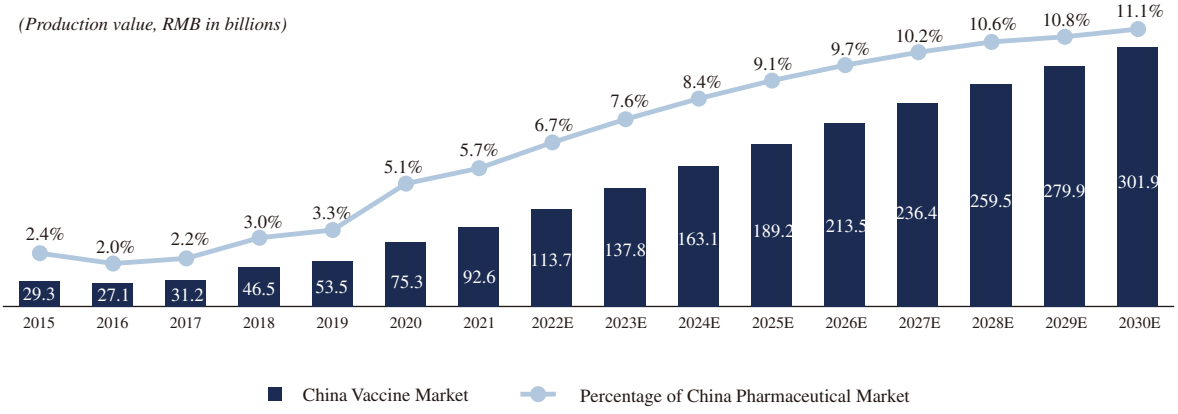
Note: Exchange rate in 2021: GBP/USD=1.3757, EUR/USD=1.1827.

Source: Financial reports of listed companies, Frost & Sullivan Analysis

The growth of the global vaccine market is mainly due to the launch of innovative vaccines and sales expansion in emerging markets, including China. As a result, the vaccine market in China is expected to experience similar growth. In terms of production value, the vaccine market in China increased from RMB29.3 billion in 2015 to RMB92.6 billion in 2021 at a CAGR of 21.2%, and is expected to grow to RMB189.2 billion in 2025 at a CAGR of 19.5% from 2021 to 2025, and further grow to RMB301.9 billion in 2030 at a CAGR of 9.8% from 2025 to 2030. The chart below illustrates the historical and forecasted vaccine market size in China for the periods indicated:

Vaccine Market in China, 2015-2030E

Period	CAGR
2015-2021	21.2%
2021-2025E	19.5%
2025E-2030E	9.8%



Notes:

(1) China's vaccine market size is measured by output value and forecasted based on annual batch issuance data. The COVID-19 vaccine market is not taken into consideration. The historical data is gathered from the National Institutes for Food and Drug Control (NIFDC). The forecasted data is based on the assumption the market is continuously driven by the unmet medical needs of the vaccine industry of China.

(2) Percentage of China pharmaceutical market is calculated based on 2020 data.

Source: Expert interviews, NIFDC, Frost & Sullivan Analysis

In terms of government policies, the Chinese government has issued several favorable policies to incentivize the development of vaccine industry. In China's 14th 5-Year Plan, it sets out the aim to expand immunization plan. In 2017, Opinions of the General Office of the State Council on Further Strengthening the Management of Vaccine Circulation and Vaccination (國務院辦公廳關於進一步加強疫苗流通和預防接種管理工作的意見) sets out principles to promote independent R&D and improve quality of vaccines to support R&D and industrialization of new vaccines, especially combination vaccine and multivalent vaccines; and financially support R&D of eligible vaccines through national science and technology programs, which also points out that media should play a crucial role in educating the public for immunization knowledge, such as the importance, safety, and effectiveness of vaccination, and increasing vaccination rate of the public. These policies are in favor of developing new vaccines, as well as assist new vaccine to enter the market.

Entry Barriers of the Human Vaccines Market in China

Entry barriers to the human vaccines market in China include (i) long development cycle, (ii) compliance with government regulations, (iii) production capacity, and (iv) capital requirement.

- *Long development cycle*. Vaccine development is an arduous process. The vaccine development process begins with initial preclinical research, followed by clinical trials to assess the efficacy and safety of the vaccine before the vaccine can obtain NMPA approval. The R&D cycle of a new vaccine can take 10-15 years to complete, which also requires large capital investment, with a low market success rate. Therefore, the complexity, time commitment and large capital requirement to effectively conduct R&D of vaccines establish high entry barriers for new market entrants in the vaccine industry.

- *Compliance with government regulations*. Due to vaccine related incidents in China in recent years, the Vaccine Administration Law of the People's Republic of China (《中華人民共和國疫苗管理法》) (the "**VAL**") was promulgated by the National People's Congress Standing Committee on June 29, 2019, which updated vaccine management to the national level, reflecting the strictest supervision. According to the latest vaccine management law, the vaccine industry is subject to strong supervision in the R&D, production, circulation and vaccination of vaccines. Increasingly stringent regulatory policies will continue to increase the barriers to enter into the vaccine industry.

- *Production capacity*. The VAL stipulates that vaccine marketing license holders should have vaccine production capacity, and approval by the drug regulatory department of the State Council is required if vaccine production capacity exceeds a certain threshold. Those who accept commissioned production shall comply with the provisions of this law and relevant state regulations to ensure the quality of their vaccines. This regulation requires vaccine marketing license holders to have their own vaccine production facilities that meet GMP requirements. The technology and funds to build GMP compliant production facilities are also barriers to enter into the vaccine market.

- *Capital requirement*. The development of a new vaccine requires large capital investment. The construction of R&D facilities and manufacturing facilities require extensive capital resources. In addition, continuous funding is needed to conduct research and clinical trials.

HERPES ZOSTER VACCINE MARKET

Overview

Herpes zoster also known as shingles, is a viral infection that causes a painful rash. It is caused by the reactivation of the varicella-zoster virus (VZV), the same virus that causes chickenpox (varicella). Symptoms include pain, itching, or tingling in the area which will later develop into a rash. Other symptoms of herpes zoster can include fever, headache, chills, and upset stomach. The most common complication of herpes zoster is postherpetic neuralgia (PHN). Approximately 9% to 34% of patients with herpes zoster have the potential risk of developing PHN. Other complications of herpes zoster may lead to serious complications involving the eye, including blindness. In rare occasions, it can also lead to pneumonia, hearing problems, brain inflammation or death.

There are three types of herpes zoster vaccines, namely live attenuated vaccines, recombinant vaccines and messenger RNA (mRNA) vaccines.

Category	Introduction	Advantages	Disadvantages
Live attenuated herpes zoster vaccine	Conventional vaccines using intact pathogens (bacteria or viruses) as antigens	• Lower production costs • Fewer side effects	• Risk of residual virulence • Not applicable for people with weakened immune systems
Recombinant herpes zoster vaccine	A vaccine produced through recombinant DNA technology. This involves inserting the DNA encoding an antigen (such as a bacterial surface protein) that stimulates an immune response into bacterial or mammalian cells, expressing the antigen in these cells and then purifying it from them.	• Induces a human immune response while avoiding other components of the pathogen causing adverse effects on human body • Safe for people with weak immune systems	• Adjuvants are needed to help stimulate the body's immune system response and booster shots are needed to achieve continuous protection
mRNA herpes zoster vaccine	The latest vaccine technology. mRNA vaccines work by introducing a piece of mRNA that corresponds to a viral protein, usually a small piece of a protein found on the virus's outer membrane. Using this mRNA blueprint, cells produce the viral protein.	• Can be quickly designed and scaled up, and the manufacturing is sequence-independent, which makes it highly adaptable to different pathogens. The cost is lower than other platforms • Effective in avoiding the risk of virus leakage and infection	• Technology is relatively new and needs more studies to validate the immunogenicity and efficacy

Source: Frost & Sullivan Analysis

According to the relevant clinical studies of the herpes zoster vaccines on the market, the effective rate of recombinant vaccines in reducing herpes zoster and PHN is higher than that of live attenuated vaccines. In October 2017, the Advisory Committee on Immunization Practices (ACIP) recommended recombinant herpes zoster vaccines for the prevention of herpes zoster and related complications in immunocompetent adults aged 50 years old and above, and for the prevention of herpes zoster and related complications in immunocompetent adults who have previously received live attenuated herpes zoster vaccine. The ACIP states that recombinant herpes zoster vaccines are superior to live attenuated herpes zoster vaccines for the prevention of herpes zoster and related complications. Currently, the criteria of herpes zoster vaccine for ineligible patients include people who have severe allergic reaction to any of the component, and live attenuated herpeszoster vaccine is not recommended for patients with immunodeficiency or immunosuppressive diseases.

Among global markets, the herpes zoster vaccination rate in the U.S. is the highest due to the earlier availability of the vaccine in the U.S., developed commercial health insurance packages and lower cost of herpes zoster vaccines. The herpes zoster vaccination rate in China is relatively low compared to the rate of U.S. Given the large patient population in China, there is great potential for the herpes zoster vaccine market to grow in the future. The number of new cases of herpes zoster in people aged 50 years old and above in China increased from 2.5 million in 2015 to 3.9 million in 2021 at a CAGR of 7.8%. It is expected to increase to 4.9 million in 2025 at a CAGR of 6.0% from 2021 to 2025, and further increase to 6.0 million in 2030 at a CAGR of 4.2% from 2025 to 2030. The vaccination rate of herpes zoster vaccine among people aged 50 years and older is expected to reach 1.9% in 2025 and 12.6% in 2030. In comparison, the number of new cases of herpes zoster in people aged 50 years old and above in the U.S. is expected to grow at a slower rate compared to China. The number of new cases of herpes zoster in the U.S. increased from 1.0 million in 2015 to 1.1 million in 2021 at a CAGR of 2.4%. It is expected to increase to 1.2 million in 2025 at a CAGR of 1.8% from 2021 to 2025, and further increase to 1.3 million in 2030 at a CAGR of 1.5% from 2025 to 2030.

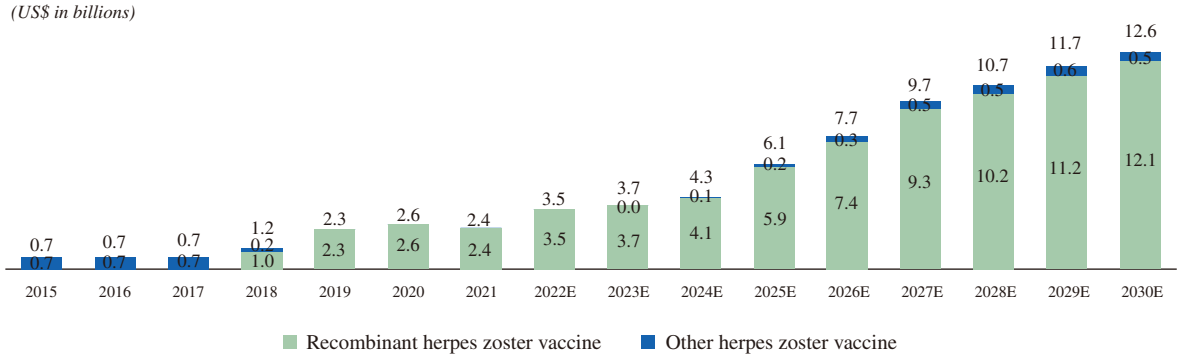
Market for Herpes Zoster Vaccines

From 2020 to 2021, due to the impact of COVID-19, governments worldwide prioritized their attention and efforts on providing vaccination of COVID-19 for the elderly, thus affecting the market demand for herpes zoster vaccines. As new herpes zoster vaccines are expected to be marketed in the future and COVID-19 is gradually brought under control, the global herpes zoster vaccine market is expected to expand.

In terms of sales revenue, the global herpes zoster vaccine market increased from US$0.7 billion in 2015 to US$2.4 billion in 2021 at a CAGR of 21.2%, and is expected to grow to US$6.1 billion in 2025 at a CAGR of 26.8% from 2021 to 2025, and further grow to US$12.6 billion in 2030 at a CAGR of 15.5% from 2025 to 2030. The chart below illustrates the historical and forecasted global herpes zoster vaccine market for the periods indicated:

Global Herpes Zoster Vaccine Market, 2015-2030E

Period	Recombinant Herpes Zoster Vaccine	CAGR
2015-2021	N/A	21.2%
2021-2025E	25.6%	26.8%
2025E-2030E	15.5%	15.5%

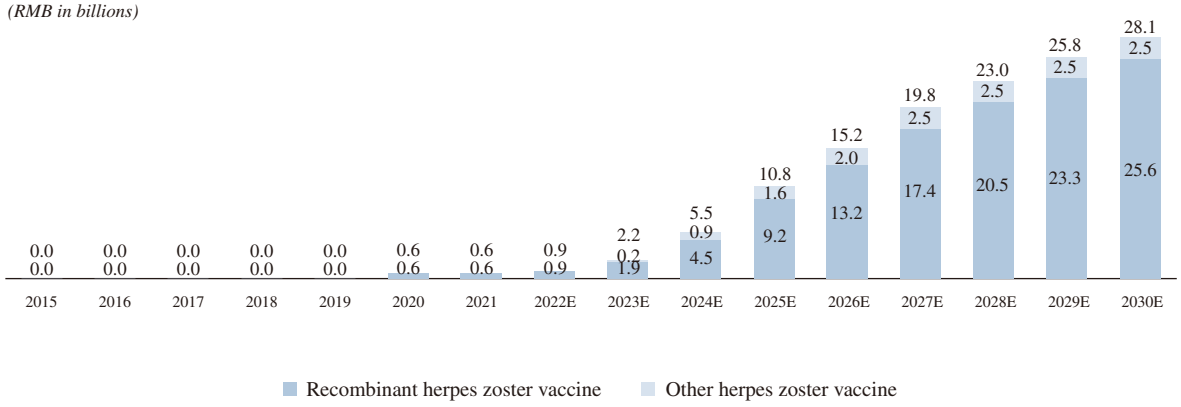


Source: Public disclosure of listed companies, expert interviews, Frost & Sullivan Analysis

According to 2022 China Herpes Zoster Vaccine Expert Consensus (帶狀皰疹疫苗預防接種專家共識), herpes zoster vaccine is recommended in order to prevent herpes zoster. The vaccination rate in people age 50 or above increased 0.04% in 2020 to approximately 0.13% in 2022. As the public awareness of herpes zoster continues to grow and the number of available herpes zoster vaccines increases, the herpes zoster vaccine market in China is expected to grow significantly. In terms of sales revenue, the herpes zoster vaccine market in China increased from nil in 2015 to RMB0.6 billion in 2021, and is expected to grow to RMB10.8 billion in 2025 at a CAGR of 103.8% from 2021 to 2025, and further grow to RMB28.1 billion in 2030 at a CAGR of 21.1% from 2025 to 2030. The chart below illustrates the historical and forecasted herpes zoster vaccine market in China for the periods indicated:

Herpes Zoster Vaccine Market in China, 2015-2030E

Period	Recombinant Herpes Zoster Vaccine	CAGR
2015-2021	N/A	N/A
2021-2025E	96.0%(1)	103.8%(2)
2025E-2030E	22.6%	21.1%



Source: Expert interviews, Frost & Sullivan Analysis

Notes:

(1) The forecasted growth is largely due to an expected decrease in the price of recombinant herpes zoster vaccines. Domestic recombinant herpes zoster vaccines are expected to be more affordable as Domestic recombinant herpes zoster vaccine candidates are expected to become commercialized during this period and their average prices are expected to decrease from RMB1,600/dose in 2021 to RMB1,100/dose in 2025, with a decline of 31%, which is expected to increase domestic acceptance of recombinant herpes zoster vaccines and contributes to the high growth. In addition, the recombinant herpes zoster vaccine market was an emerging market as Shingrix® only entered China in 2020, and the market was RMB0.6 billion in 2021. With continuing market education and increasing acceptance of herpes zoster vaccine, the market size of herpes zoster vaccine in China is expected to increase rapidly. Since the market size of herpes zoster vaccine in China relatively was small in 2021, the rapid growth would lead to a higher CAGR.

(2) The forecasted growth is largely due to (a) increasing vaccination rate: the vaccination rate of herpes zoster vaccine in China was only 0.1% in 2021 and the first herpes zoster vaccine, Shingrix®, was approved in China in April 2020. The vaccination rate is expected to increase to 1.9% in 2025. Given the large population base in China, the number of new cases of herpes zoster is relatively large, amounting to 3.9 million in 2021, which is expected to increase to 4.9 million in 2025 due to the growing aging population in China. In 2025, the number of people who have received herpes zoster vaccine is expected to reach 10.4 million, increasing from 0.4 million in 2021; (b) launch of new vaccines in the next few years: at present, Shingrix® and BCHT Biotechnology's Live Attenuated Herpes Zoster Vaccine are the only two herpes zoster vaccines available in China while other domestic herpes zoster vaccine candidates are expected to be commercialized in this period, which will contribute to the growth of the market; (c) expansion of eligible patients: Shingrix® is used for adults aged 50 years and older in China. Domestic herpes zoster vaccine candidates are expected to expand to adults aged 40 years and older.

Growth Drivers of the Global Herpes Zoster Vaccine Market

Growth drivers of the global herpes zoster vaccine market include (i) ongoing aging population, (ii) increasing number of new cases of shingles, (iii) increased public awareness and (iv) lack of effective treatment.

- *Ongoing aging population*. With declining fertility and increasing average life expectancy, the number of people aged 50 years old and above is growing at a considerable rate and is expected to continue to do so in the future, with the trend towards population aging becoming more pronounced. The global population of people aged 50 years old and above is expected to reach 2,330 million by 2030, representing approximately 27.3% of the total global population. By 2030, the number of people in China aged 50 years old and above is expected to reach 570 million, representing approximately 39.0% of the total population in China. The aging population is susceptible to the deterioration of the immune and metabolic system and is a high risk group for herpes zoster. An increasingly aging demographic will be one of the key drivers for the rapid growth of the herpes zoster vaccine market.

- *Increasing number of new cases of shingles*. Among the population over 50 years old, the number of new herpes zoster cases in China, the United States, and Europe reached 3.9 million, 1.1 million, and 2.0 million in 2021, respectively. Due to low vaccination rates, the number of new cases of herpes zoster still shows a growing trend, and the total number of patients with herpes zoster will continue to expand in the future. In addition, along with changing lifestyles, high work stress and low immunity, people under 50 years old are also prone to getting shingles.

- *Increased public awareness*. The steady growth in the global economy has led to increasing per capita disposable income, which in turn has increased the individual healthcare spending on vaccinations. In addition, the level of health awareness has been increasing in recent years, with the accumulation of knowledge and promotion of disease prevention. In the post-COVID-19 era, the health of the elderly has also attracted social attention. Shingles occurs frequently in people aged over 50. When people have weak immune systems, it can cause severe pain and seriously affect the quality of life of the elderly. In the past, vaccines mainly protected children's health and prevented various infectious diseases among children. With the continuous marketing of new vaccines, including herpes zoster vaccines, they will meet the prevention needs of different age groups. For instance, in a survey conducted in Shanghai, the awareness of herpes zoster vaccine in local people aged 50 and above increased from 30% in 2020 to 42% in 2021. The awareness and acceptance of vaccination is expected to rise in the wake of the COVID-19 pandemic, further contributing to developing the vaccine market and increasing vaccination rates.

- *Lack of effective treatment*. Herpes zoster is accompanied by complications such as neuralgia. The pain can be dull, convulsive or throbbing, which disturbs sleep, mood, work and daily life. In severe cases, it may lead to depression. Elderly and frail patients may experience more pain. In addition, herpes zoster lacks quick and effective treatments. According to the *2018 Clinical Guideline for Herpes Zoster* in China, at present, there is no specific drug for herpes zoster. Current treatment goals for herpes zoster are to relieve acute pain, shorten the duration of skin lesions, prevent skin lesions from spreading and prevent or alleviate complications such as postherpetic neuralgia ("**PHN**"). Existing treatment methods primarily include antiviral drugs, glucocorticoid therapy and analgesic treatment. Antiviral drugs are commonly used in the clinical treatment of herpes zoster and can shorten the course of disease, accelerate the healing of rashes, prevent the formation of new rashes,

and prevent the spread of viruses to the viscera. Glucocorticoid therapy, on the hand other hand, is still controversial. While systemic administration of glucocorticoids in the early stages of an acute herpes zoster attack can inhibit the inflammatory process, shorten the duration of acute pain and skin healing time, it is not effective for pain caused by PHN. Analgesic treatment primarily includes prescription of acetaminophen, nonsteroidal anti-inflammatory drugs, or tramadol, for mild to moderate pain, and prescription of morphine, oxycodone, or neuropathic pain medications such as calcium channel modulators like gabapentin and pregabalin, for moderate to severe pain. Vaccination can prevent herpes zoster and largely reduce the burden of related diseases.

Competitive Landscape

As of the Latest Practicable Date, there were four herpes zoster vaccines marketed globally, namely Merck & Co., Inc.'s Zostavax®, GlaxoSmithKline plc's Shingrix®, SK Chemicals Co., Ltd.'s SkyZoster and BCHT Biotechnology's Live Attenuated Herpes Zoster Vaccine. Among them, SkyZoster is only sold in Korea with a market share accounted for approximately 1.0% of global herpes zoster market, and BCHT Biotechnology's Live Attenuated Herpes Zoster Vaccine is only sold in China. Due to the low effectiveness of Zostavax® as a herpes zoster prophylaxis and its weakened market competitiveness, it has been discontinued production. In 2021, Shingrix® captured almost 100% of the global market share in terms of sales revenue, and is the only commercially available herpes zoster vaccine in China. The following table sets forth details of Shingrix®, Zostavax® and BCHT Biotechnology's Live Attenuated Herpes Zoster Vaccine:

	GlaxoSmithKline	Merck & Co.	BCHT Biotechnology
Product name	Shingrix®	Zostavax®	Herpes Zoster Vaccine
Type of technology	Recombinant	Live attenuated	Live attenuated
Effectiveness reducing herpes zoster	50-59 years old: 96.6% 60-69 years old: 97.4% 70+ years old: 91.3%	50-59 years old: 70% 60-69 years old: 64% 70-79 years old: 41% ≥80 years old: 18%	N/A
Effectiveness reducing postherpetic neuralgia	≥50 years old: 91.2% ≥70 years old: 88.8%	≥60-69 years old: 65.7% ≥70 years old: 66.8%	N/A
Date of approval	United States: October 20, 2017 Europe: March 28, 2018 China: May 22, 2019	United States: February 24, 2006 Europe: May 19, 2006	China: January 29, 2023
Price	RMB1,600/dose in China* approximately US$120/dose overseas	Approximately US$135/dose	N/A
Vaccine administration procedure	Two doses, second dose administered 2-6 months after first dose	One dose	One dose

Source: CDC, FDA, literature search, Frost & Sullivan Analysis

* As of the Latest Practicable Date, there was no public information regarding the effectiveness and price of BCHT Biotechnology's Live Attenuated Herpes Zoster Vaccine.

* For a new foreign vaccine to enter the Chinese market, clinical trials in China are required, which would result in additional expenses for GSK. In addition, Shingrix® is the first herpes zoster vaccine commercialized in China, which requires market education and establishment of the sales team to promote the new vaccine, and this would incur additional expenses as well. Therefore, based on the large initial investment, it is reasonable that the selling price of Shringrix is higher in China. In the foreseeable future, it is expected that more herpes zoster vaccines will be commercialized and enter the market in China. In order to compete for more market share, it is reasonable that the price of Shringrix will experience a decreasing trend. For overseas market, it is the similar situation for Shringrix to lower the price in the future since more herpes zoster vaccines are expected to enter the global market.

In a BALB/c mice study, our LZ901 induced a stronger cellular immune response with higher expression of multiple types of immune cell activating biomarkers compared to Shingrix®. In the Phase I clinical trial for LZ901 in China, LZ901 was able to stimulate the rapid production of higher levels of anti-VZV antibodies after the first vaccination and similar levels of anti-VZV antibodies after the full course of vaccination compared to Shingrix® based on humoral response data. In addition, LZ901 was able to stimulate helper (CD4+) T cells to express significantly higher levels of multiple types of immune cell activating biomarkers and cytotoxic (CD8+) T cells to express slightly higher levels of multiple types of immune cell activating biomarkers compared to Shingrix® based on cellular immune response data from the Phase I clinical trial for LZ901 in China, indicating that the immunogenicity of LZ901 is not weaker than Shingrix® and LZ901 provides strong protection against shingles.

LZ901 has a different antigen structure and a formulation that uses a different adjuvant compared to Shingrix®. The incidence of adverse reactions related to aluminum hydroxide adjuvant used in LZ901 is expected to be lower than the oil-based adjuvant used in Shingrix®. After receiving an injection of Shingrix®, the vast majority of subjects experience temporary nodules at the injection site or nodules that take a long time to resolve and pain at the injection site. Similarly, the incidence of side reactions of our LZ901 is expected to be lower than that of Shingrix®, and the incidence of temporary nodules at the injection site or local pain should also be lower than that of Shingrix®.

As of the Latest Practicable Date, there were four herpes zoster vaccines under development in China and five herpes zoster vaccine candidates at the clinical stage in Australia, the Philippines and the U.S.. The following chart sets forth details of the herpes zoster vaccines under development in China:

Vaccine Name	Technology	Company	R&D Progress	Clinical Application Country	Date of Clinical Approval	Date of Phase I Clinical Trial*
Live attenuated herpes zoster vaccine	Live attenuated	Shanghai Institute of Biological Products (上海生物製品研究所)	Phase II (completed)	China	August 21, 2017	November 20, 2018
Recombinant herpes zoster vaccine (CHO)	Recombinant	Luzhu Biotech (綠竹生物)	Phase II	China	August 4, 2021	January 15, 2022
			Phase I	U.S.	July 13, 2022	February 2023
Recombinant herpes zoster vaccine (CHO)	Recombinant	Ab&B Bio-Tech (中慧元通)/ Easyway (上海怡道)	Phase I/II	China	May 6, 2020	December 13, 2021
Recombinant herpes zoster vaccine (CHO)	Recombinant	MAXVAX Biotechnology (邁科康生物)	Phase I	China	January 4, 2022	October 21, 2022

Note: * Date when the phase of clinical trial was first published by the CDE.

Source: *Center for Drug Evaluation (CDE), public disclosure of listed companies, Frost & Sullivan Analysis*

VARICELLA VACCINE MARKET

Overview

Varicella also known as chickenpox, is an acute infectious disease caused by VZV. Humans are the only host of VZV. VZV enters the host through the respiratory tract and conjunctiva. It replicates at the site of entry in the nasopharynx and in regional lymph nodes. A rash is often the first sign of disease in children. Adults may have 1 to 2 days of fever and malaise before a rash. In unvaccinated individuals, generalized and pruritic rash progresses rapidly.

Since varicella is a highly infectious disease and China has a higher population density compared to the U.S., the incidence rate of varicella in China is higher than that of the U.S. The incidence of varicella in China increased from 33.9 cases per 100,000 population in 2015 to 88.8 cases per 100,000 population in 2021 at a CAGR of 17.4%, and is expected to increase to 126.6 cases per 100,000 population in 2025 at a CAGR of 9.3% from 2021 to 2025, and further increase to 154.0 cases per 100,000 population in 2030 at a CAGR of 4.0% from 2025 to 2030. In comparison, the incidence rate of varicella in the U.S. is lower since the U.S. was the first country to recommend universal routine varicella vaccination. The incidence rate of varicella in the U.S. decreased from 3.8 cases per 100,000 population in 2015 to 2.8 cases per 100,000 population in 2021 at a CAGR of -4.8%, and is expected to decrease to 2.3 cases per 100,000 population in 2025 at a CAGR of -4.6% from 2021 to 2025, and further decrease to 1.9 cases per 100,000 population in 2030 at a CAGR of -4.6% from 2025 to 2030.

Types of Varicella Vaccines

There are two types of commercialized varicella vaccines, monovalent vaccines, consisting of live attenuated vaccines and recombinant vaccines, and combination vaccines. Live attenuated vaccines and combination vaccines contain the Oka strain of live attenuated virus. Monovalent vaccines have demonstrated less severe side effects while combination vaccines have demonstrated higher efficacy. As of the Latest Practicable Date, there was no recombinant varicella vaccine approved in the market. The recombinant varicella vaccine has a higher protective effect. While inducing a human immune response, it can prevent other components of the pathogen from causing adverse effects on the human body.

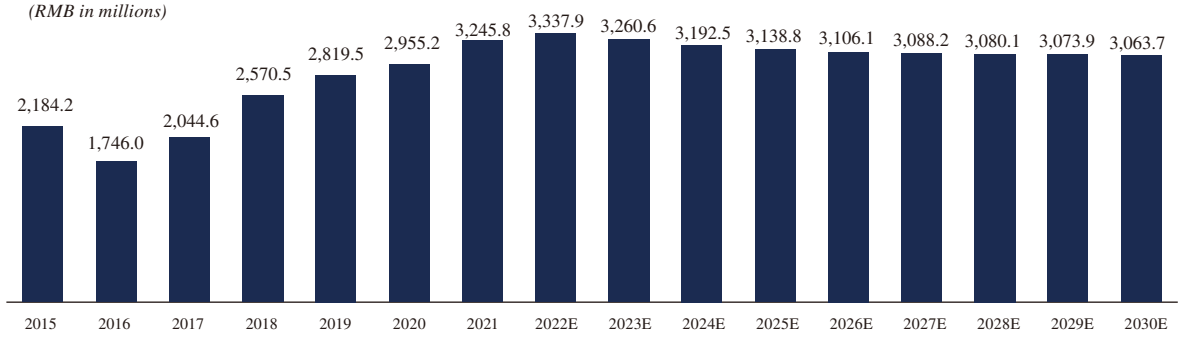
Market for Varicella Vaccines

In China, children aged five to seven years old are most likely to be infected with varicella. Currently, varicella vaccines are mostly for children aged from 12 months to 12 years old, which covered approximately 213.1 million population in China in 2021 and is expected to decrease to 190.0 million in 2030. In 2020, the vaccination rate among children aged 1 to 14 years old was approximately 52.7% and 11.4% for first and second dose, respectively. Prior to 2012, China recommended only one dose of varicella vaccine. Since 2012, the PRC government began to promote the administration of two doses of varicella vaccine, which contributed to the growth of the varicella vaccine market in China in the past few years. However, the decline in birth rate will impact the future growth of the varicella vaccine market in China. The criteria of varicella vaccine for ineligible patients are people who have severe allergic reaction to any of the component, patients with immunodeficiency or immunosuppressive diseases, people with encephalopathy, uncontrolled epilepsy and other progressive neurological diseases, etc.

The varicella vaccine market in China increased from RMB2,184.2 million in 2015 to RMB3,245.8 million in 2021 at a CAGR of 6.8%, and is expected to decline to RMB3,138.8 million in 2025 at a CAGR of -0.8% from 2021 to 2025, and further decline to RMB3,063.7 million in 2030 at a CAGR of -0.5% from 2025 to 2030. The expected decline from 2021 to 2030 is largely due to the declined birth rate as varicella vaccines in China are for children aged under 12, partially offsetting the expected increase in vaccination rate. The chart below illustrates the historical and forecasted varicella vaccine market in China for the periods indicated:

Varicella Vaccine Market in China, 2015-2030E

Period	CAGR
2015-2021	6.8%
2021-2025E	-0.8%
2025E-2030E	-0.5%



Source: Public disclosure of listed companies, expert interviews, NIFDC, Frost & Sullivan Analysis

Competitive Landscape

As of the Latest Practicable Date, there were five commercialized varicella vaccines marketed in China, which are all based on the technology of live, attenuated varicella-zoster virus derived from the Oka strain. The following table sets forth details of the approved varicella vaccines in China:

Commercialized Varicella Vaccines in China

Company	Technology	Vaccine Administration Procedure	Approval Date	Price, per Dose, 2021	Sales Revenue, 2021 (RMB million)	Market Share, 2021
Changchun Keygen Biological Products	Live attenuated	One dose administered for 12 month and older	March 30, 2007	RMB145.5-160.5	1,078.2	33.2%
BCHT Biotechnology	Live attenuated	One dose administered for 1-12 years of age; 2 dose administered for 13 years and older	February 4, 2008	RMB90-160.5	1,020.3	31.4%
Shanghai Institute Of Biological Products	Live attenuated	One dose administered for 12 month – 12 years old	November 7, 2006	RMB90-160.5	674.7	20.8%
RongSheng Biotech	Live attenuated	One dose administered for 12 months – 12 years old	October 25, 2016	RMB136-157	270.6	8.3%
Sinovac	Live attenuated	12 months – 12 years of age: One dose One booster dose can be administered when deemed necessary	December 18, 2019	RMB90	202.0	6.3%

Source: Public disclosure of listed companies, NMPA, Frost & Sullivan Analysis

Currently, all the varicella vaccines in the global market are developed by live attenuated technology. In 2021, major manufacturers of varicella vaccine included Merck & Co., GSK, Changchun Keygen Biological Products, BCHT Biotechnology and SK Bioscience. Merck & Co. had the largest global market share of 55.7% in 2021. The following table sets forth details of major manufacturers of varicella vaccine:

Company Name	Product	Technology	Market Share, in 2021	Price, per Dose, in 2021
Merck & Co.	Varivax & ProQuad	Live attenuated	55.7%	U.S. CDC Price: Varivax: $122.67-150.98 ProQuad: $153.507-250.02
GSK	Varilrix & Priorix Tetra	Live attenuated	9.3%	Price in Australia: Varilrix: AUD 64.95 Priorix Tetra: AUD 68.95
Changchun Keygen Biological Products	Varicella Vaccine, Live	Live attenuated	5.3%	RMB145.5–160.5
BCHT Biotechnology	Varicella Vaccine, Live	Live attenuated	5.1%	RMB90-160.5
SK Bioscience	Sky Varicella	Live attenuated	3.9%	RMB90-160.5
Others	NA	NA	20.7%	NA

HUMAN RABIES VACCINE MARKET

Overview

Rabies is a vaccine-preventable viral disease often transmitted through the bite of a rabidly infected animal. Rabies is caused by the *Rabies lyssavirus*, which includes the rabies virus and the Australian bat rabies virus. The rabies virus infects the central nervous system of mammals, eventually leading to brain disease and death. Rabies is a contagious disease with a very high mortality rate, which is why countries around the world are dedicated to eliminating rabies. The disease, which is nearly always fatal, is preventable by vaccines given either before and/or after exposure to a rabid animal. Numerous factors including the high cost of vaccines, the relative complexity of post-exposure vaccination protocols requiring multiple doses of vaccine, and insufficient surveillance contribute to the estimated 59,000 human deaths caused by rabies each year, according to the WHO.

According to the Center for Disease Control and Prevention (CDC) in China and in the U.S., the number of new human rabies cases in China and the U.S. was 2,048 cases and 2 cases in 2010, respectively, and decreased to 157 cases and 5 case in 2021, respectively. In the U.S., rabies is prevented through the vaccination of animals, while in China, humans are vaccinated. Despite the rapid decline in the number of cases in China, the number of rabies cases in China is still at a higher level compared to that of the U.S.

Types of Human Rabies Vaccines

Currently there are four types of commercialized rabies vaccines, including hamster kidney cell vaccine, purified chick embryo cell vaccines (PCEC), purified Vero cell vaccines (PVCV) and human diploid cell vaccines (HDCV), of which hamster kidney cell vaccines are less popular in the global market. In 2021, there was no purified chick embryo cell (PCEC) human rabies vaccines in China. As for purified Vero cell vaccines (PVCV), the key manufactures are Liaoning Chengda Biotechnology (with market share of 54.3%) and Rongan Biological (with market share of 24.4%). As for human diploid cell vaccines (HDCV), Chengdu Kanghua Biological Products captures 100% market share. The following tables set forth the various types of cell culture vaccines:

Cell Line	Hamster Kidney Cell	PCEC	PVCV
Features	The first approved cell culture rabies vaccine was the hamster kidney cell rabies vaccine, which was developed in China in 1980 with an aluminum adjuvant and the strain being the Beijing aG strain, inactivated with formaldehyde.	PCEC vaccine was cultured in primary chicken embryo fibroblasts with the Flury LEP-C25 virus strain, inactivated with 0.025% β-propiolactone and then concentrated and purified using density gradient centrifugation.	The Vero cell line, was established in 1962 and supports infection with multiple genotypes of the Lisa virus genus. PVCV vaccine was first approved in Europe and now are being massively producing in many developing countries.
Advantages	Mild adverse effects, relatively good efficacy and safety, as well as relatively low price.	Clinical experience in over 60 countries over the last 30 years has shown that the vaccine is immunogenic, effective and safe.	Can be grown and infected on microcarriers and cultured in fermentation instillations, immortalized cell lines have an almost unlimited growth capacity and can be produced on a large scale.
Disadvantages	Less effective in terms of safety and efficacy comparing to HDCV and PVCV rabies vaccines.	Currently no PCEC vaccine available in China. It is difficult to be massively produced and relatively expensive.	Immortalized cell lines have potential cancer risk.
Mainly Used in	China	Australia, Europe, India and U.S.	China, India
Major manufactures	Henan Grand Biopharmaceutical, Zhongke Biopharm	GSK, ChiroRab	Liaoning Chengda Biotechnology, Rongan Biological, Sanofi Pasteur, Indian Immunologicals, Serume Institute of India

Cell Line	HDCV	Recombinant Protein
Features	The first human diploid cell line, WI38, was established in 1961 to avoid problems arising from the use of primary tissue culture, such as allergy to animal proteins. It is currently produced using MRC5 human embryonic fibroblasts, inoculated with the Pitman Moor L503 3M strain.	Currently, there is no recombinant rabies vaccine launched in the market. All the products are in R&D. Only the product from CPL Biologicals, a biopharma company in India is recorded to enter Phase III clinical experiments. The non-replicating virus-based vaccine uses a viral vector that cannot be replicated in the host and can express the G protein of the rabies virus, thereby causing an immune response.
Advantages	Recommended by the WHO as the "gold standard" rabies vaccine. HDCV vaccine induces a more intense immune response in test animals and humans and is less likely to cause adverse reactions.	The vaccine produced by this technology has a high degree of safety for the host body.
Disadvantages	It has high cost, therefore, is mainly used in developed countries. In China, there is only one manufacturer, Chengdu Kanghua Bio, which listed its HDCV rabies vaccine in 2015.	The production cost of the vaccine produced by this technology will be higher, so the price will be higher in the future.
Mainly Used in	China, Europe, U.S., Australia	/
Major manufactures	Chengdu Kanghua Biological Products, Sanofi Pasteur	/

Source: Frost & Sullivan Analysis

Market for Pre-Exposure Human Rabies Vaccine in China

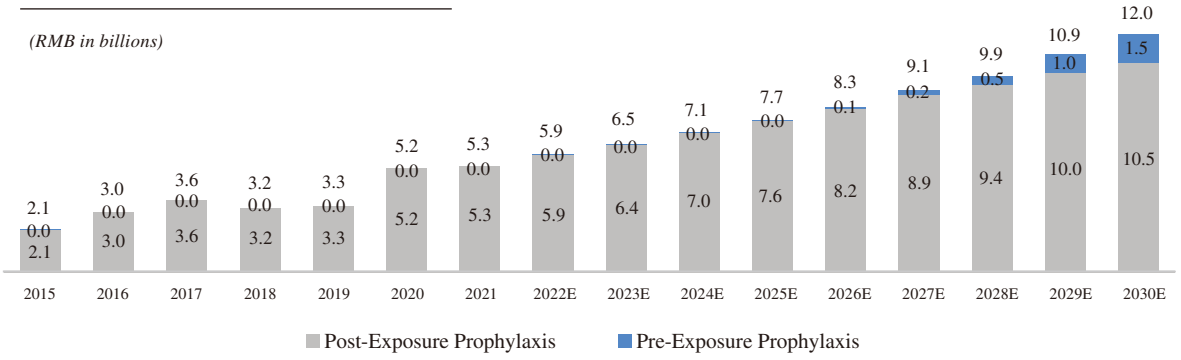
Currently, most human rabies vaccines marketed in China are for post-exposure prophylaxis (PEP). Although this type of vaccine can also be given prior to exposure, most people still receive rabies vaccines after being bitten or scratched by animals such as cats and dogs. In addition, human rabies vaccination is used for pre-exposure prophylaxis (PrEP) for populations at high risk of rabies virus exposure, including sub-populations in highly endemic settings with limited access to timely and adequate PEP, individuals at occupational risk, and travelers who may be at risk of exposure. People who are at an occupational risk of rabies virus exposure account for a small portion of the total vaccine recipients, including Centers for Disease Control and Prevention staff, veterinary clinic staff and dog trainers. In 2021, approximately 15 million people in China received human rabies vaccine. In the future, the market for human rabies vaccines as a PrEP can be expanded to other groups of people with a potential risk of rabies virus exposure, including courier and food delivery staff and other potential target groups. Since rabies is nearly always fatal, there is no criteria for post-exposure vaccination. The criteria of pre-exposure human rabies vaccine for ineligible patients include people who have severe allergic reaction to any of the component, patients with immunodeficiency or immunosuppressive diseases, etc.

The human rabies vaccine market in China increased from RMB2.1 billion in 2015 to RMB5.3 billion in 2021 at a CAGR of 16.8% and is expected to grow to RMB7.7 billion at a CAGR of 9.5% from 2021 to 2025, and further increase to RMB12.0 billion in 2030 at a CAGR of 9.2% from 2025 to 2030. The growth of human rabies vaccine market in China is largely due to the increasing demand of human rabies vaccine. The number of pet cats and pet dogs has been growing rapidly these years and is expected to grow in the future, generating demand for human rabies vaccine. The pre-exposure human rabies vaccine market in China increased from RMB4.2 million in 2015 to RMB10.7 million in 2021 at a CAGR

of 16.8% from 2015 to 2021, and is expected to increase to RMB2,960.2 million in 2035 at a CAGR of 49.4% from 2021 to 2035. The chart below illustrates the historical and forecasted rabies vaccine market in China for the periods indicated:

Human Rabies Vaccine Market in China, 2015-2030E

Period	CAGR
2015-2021	16.8%
2021-2025E	9.5%
2025E-2030E	9.2%

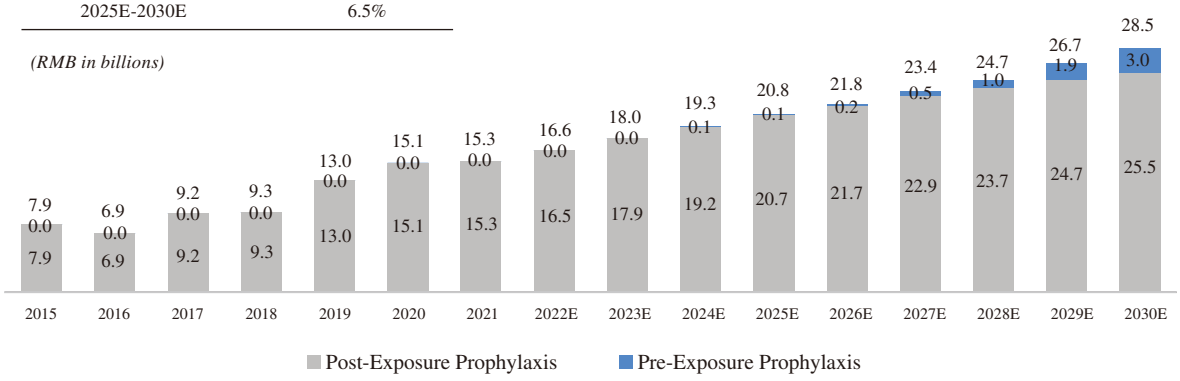


Source: Company public disclosure, NMPA, DataYes Inc., Frost & Sullivan Analysis

The global human rabies vaccine market increased from RMB7.9 billion in 2015 to RMB15.3 billion in 2021 at a CAGR of 11.6% and is expected to grow to RMB20.8 billion at a CAGR of 8.0% from 2021 to 2025, and further increase to RMB28.5 billion in 2030 at a CAGR of 6.5% from 2025 to 2030. The chart below illustrates the historical and forecasted global rabies vaccine market for the periods indicated:

Global Human Rabies Vaccine Market, 2015-2030E

Period	CAGR
2015-2021	11.6%
2021-2025E	8.0%
2025E-2030E	6.5%



Source: Company public disclosure, Frost & Sullivan Analysis

Growth Drivers of Pre-Exposure Human Rabies Vaccine Market in China

Growth drivers of the Pre-Exposure human rabies vaccine market include (i) increasing number of pet owning families creating large potential demand (ii) favorable policies and (iii) enhanced awareness of preventative immunization.

- *Increasing number of pet owning families creating large potential demand.* In recent years, with the continuous growth of consumption and increasing attention to pets, the number of pet dogs and cats in China has been increasing and approaching 100 million. Since dogs are the main source of human rabies deaths in China, the high number of pet dogs exposes dog-owning families to the potential risk of rabies.

- *Favorable policies. Countries around the world have been working to eliminate rabies.* In 2018, the WHO released "Zero by 30" with the goal of effectively using vaccines, medicines, tools and technologies to block rabies transmission and reduce the risk of death and implement the Global Strategic Plan to end human deaths from dog-mediated rabies by 2030. In China, the Technical Guidelines for Rabies Prevention and Control (2016 edition), published by the CDC in 2016, provided the guidance and recommendations for pre- and post-exposure vaccination and the use of passive immunization preparations. Meanwhile, in 2021, China's 14th Five-Year Plan proposes to improve the fast-track review and approval mechanism for innovative drugs, vaccines and medical devices. Favorable policies will facilitate the promotion of rabies vaccines, thus promoting the sustainable development of the human rabies vaccine industry.

- *Enhanced awareness of preventative immunization.* Rabies is a disease with a nearly 100% mortality rate after onset of symptoms, causing a heavy disease burden in countries such as China. Therefore, increasing awareness of the hazard of rabies and the preventative immunization of human rabies vaccines are important for the control and elimination of rabies.

Competitive Landscape

In 2021, Liaoning Chengda Biotechnology and Chengdu Kanghua Biological Products had more than half of the market share of the human rabies vaccine market in China. The following table sets forth details of the competitive landscape of the human rabies vaccine industry in terms of sales revenue and market share in China in 2021:

Company Name	Product	Sales Revenue in 2021 (billion RMB)	Market Share in 2021 (%)
Liaoning Chengda Biotechnology	Rabies Vaccine (Vero Cell) for Human Use	2.1	39.0%
Chengdu Kanghua Biological Products	Rabies Vaccine (Human diploid cell) for Human Use, Freeze-dried	1.3	23.7%
Rongan Biological	Rabies Vaccine (Vero Cell) for Human Use	0.9	17.5%
Changchun Zhuoyi Biological	Rabies Vaccine (Vero Cell) for Human Use, Freeze-dried	0.4	7.8%
Zhongke Biopharm	Rabies Vaccine (Hamster Kidney Cell) for Human Use	0.1	2.0%
Others	/	0.5	10.0%

Notes:

(1) As of the Latest Practicable Date, there were 12 human rabies vaccines registered in the CDE, while 3 of them had not generated any revenue in 2021. This excludes human rabies vaccines which did not have any batches issued by the NMPA in the last five years.

(2) Market share is calculated in terms of total market size of human rabies vaccine in China.

Source: Financial reports of listed companies, Frost & Sullivan analysis

As of the Latest Practicable Date, there were 13 commercialized human rabies vaccines marketed in China (three of them have not generated any revenue in 2021 and one was approved in January 2023), which can be injected in both adults and children. The following table sets forth details of the commercialized human rabies vaccines in China:

Commercialized Human Rabies Vaccines in China

Manufacturer	Cell Line	Administration	Approval Date	Price, 2021
Hualan Bio	PVCV	Pre-exposure: Three doses Post-exposure: Four doses (2-1-1) or five doses	January 29, 2023	/
Shandong Yidu Biotechnology		Pre-exposure: Three doses Post-exposure: Four doses (2-1-1) or five doses	July 12, 2021	/
Changchun Institute of Biological Products		Four-dose or five dose	April 30, 2021	/
Changchun Zhuoyi Biological		Pre-exposure: Three doses Post-exposure: Five doses	November 23, 2016	RMB65-93
Dalian Aleph Biomedical		Pre-exposure: Three doses Post-exposure: Five doses	September 28, 2016	RMB58.5-91.0
Liaoning Chengda Biotechnology	PVCV	Pre-exposure: Three doses Post-exposure: Four doses (2-1-1) or five doses	March 6, 2007	Frozen-dried: RMB60-258.5 Non-frozen-dried: RMB42.09-104
Rongan Biological		Pre-exposure: Three doses Post-exposure: Five doses	September 30, 2007	RMB53.85-87
Promise Biological		Pre-exposure: Three doses Post-exposure: Five doses	May 8, 2008	RMB53
Jilin Maifeng Biopharmaceutical		Pre-exposure: Three doses Post-exposure: Five doses	January 9, 2008	/
Liaoning Yisheng Biopharma		Pre-exposure: Three doses Post-exposure: Five doses	November 6, 2006	RMB68.5-243.5
Henan Grand Biopharmaceutical	Hamster Kidney Cell	Pre-exposure: Three doses Post-exposure: Five doses	June 12, 2007	RMB46.2-89.5
Zhongke Biopharm		Pre-exposure: Three doses Post-exposure: Five doses	May 28, 2007	RMB58.8-95
Chengdu Kanghua Biological Products	HDCV	Pre-exposure: Three doses Post-exposure: Five doses	April 28, 2012	RMB275-320

Note:

* *Excluding human rabies vaccines in China that did not have any batches issued by the NMPA in the last five years.*

Source: Public disclosure of listed companies, DataYes Inc., NMPA, Frost & Sullivan Analysis

ADALIMUMAB INJECTABLE MARKET

Overview of Anti-tumor Necrosis Factor (TNF)-α Monoclonal Antibody (mAb) and Immune-Mediated Inflammatory Diseases (IMIDs)

TNF-α is a key regulator of innate immunity and plays an important role in the regulation of the immune responses against intracellular bacteria and certain viral infections. However, the natural occurring cytokines, such as TNF, can contribute to numerous pathological situations in related to inflammatory and immune responses. These include IMIDs including rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and severe chronic plaque psoriasis.

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and other areas of the body, for which there is currently no cure. The incidence of rheumatoid arthritis in China increased from 5,773.4 thousand in 2015 to 6,001.6 thousand in 2021 at a CAGR of 0.6% from 2015 to 2021, and is expected to increase to 6,161.3 thousand in 2025 at a CAGR of 0.7% from 2021 to 2025, and further increase to 6,409.1 thousand in 2030 at a CAGR of 0.8% from 2025 to 2030.

Crohn's disease is an incurable chronic inflammatory bowel disease. It is characterized by mucosal ulceration and inflammation, which may occur anywhere along the gastrointestinal tract but most commonly affect the distal small intestine. The inflammation caused by Crohn's disease often spreads deep into the layers of the affected bowel tissue and can be both painful and debilitating, and sometimes may lead to life-threatening complications. The incidence of Crohn's disease in China increased from 81.1 thousand in 2015 to 160.9 thousand in 2021 at a CAGR of 12.1% from 2015 to 2021, and is expected to increase to 215.9 thousand in 2025 at a CAGR of 7.6% from 2021 to 2025, and further increase to 282.7 thousand in 2030 at a CAGR of 5.5% from 2025 to 2030.

Psoriasis is a common skin condition that speeds up the life cycle of skin cells. Psoriasis is a chronic disease for which there is currently no cure. It causes cells to build up rapidly on the surface of the skin. The extra skin cells form scales and red patches that are itchy and sometimes painful. The incidence of psoriasis in China increased from 6,460.7 thousand in 2015 to 6,672.3 thousand in 2021 at a CAGR of 0.5% from 2015 to 2021, and is expected to increase to 6,789.0 thousand in 2025 at a CAGR of 0.4% from 2021 to 2025, and further increase to 6,853.0 thousand in 2030 at a CAGR of 0.2% from 2025 to 2030.

Ankylosing spondylitis is a type of arthritis that causes inflammation in certain parts of the spine, for which there is currently no clear cause or cure. The incidence of ankylosing spondylitis in China increased from 3,780.3 thousand in 2015 to 3,916.1 thousand in 2021 at a CAGR of 0.6% from 2015 to 2021, and is expected to increase to 3,986.0 thousand in 2025 at a CAGR of 0.4% from 2021 to 2025, and further increase to 4,054.2 thousand in 2030 at a CAGR of 0.3% from 2025 to 2030.

Anti-TNF-α mAb is a new generation therapy that treats IMIDs with high effectiveness, safety and convenient administration methods. The interaction of soluble and transmembrane bioactive forms of human TNF-α binding prevents the binding of TNF-α to its receptors, thereby inhibiting the biological activity of TNF-α. Anti-TNF-α mAb can restrict TNF-α's ability to activate T cells, effectively neutralizing TNF-α bioactivity and inducing the apoptosis of TNF-expressing cells.

Market for Adalimumab

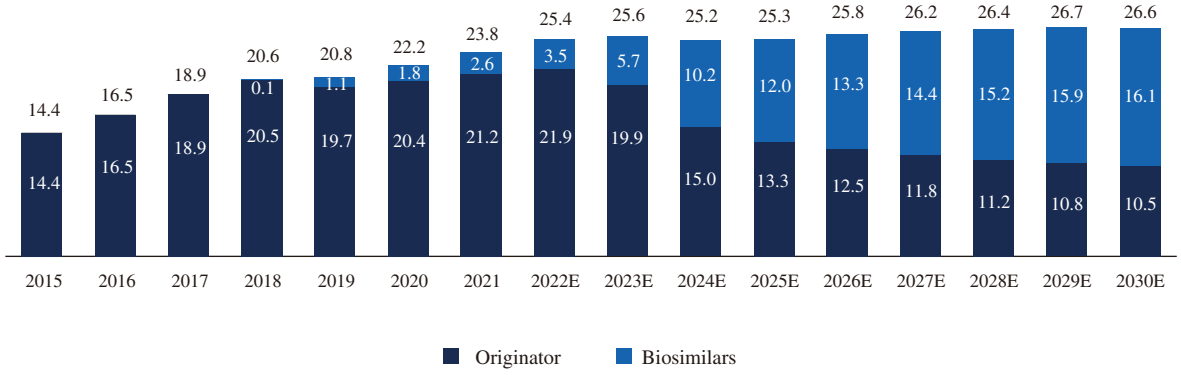
Humira®, generically known as adalimumab, is a TNF-α inhibitor for the treatment of autoimmune diseases. In December 2002, Humira® was approved by the U.S. Food and Drug Administration ("**FDA**") for the treatment of rheumatoid arthritis. Subsequent indications approved by the FDA include psoriatic arthritis, ankylosing spondylitis and Crohn's disease. Most of the indications are chronic diseases that require long-term regular treatment. Given the wide range of indications, Humira® has been ranked first in global prescription drug sales for nine consecutive years and its efficacy in the treatment of autoimmune diseases has been widely verified. Adalimumab and its biosimilars and biosimilar candidates are facing fierce competitions against each other in their therapeutic segments. K3, also a biosimilar of adalimumab, is expected to compete with Humira®, Anjianning (安建寧), Handayuan (漢達遠), Taibowei (泰博維), Junmaikang (君邁康) and other adalimumab biosimilars that have been launched or currently under development in China.

In terms of sales revenue, the global adalimumab market increased from US$14.4 billion in 2015 to US$23.8 billion in 2021 at a CAGR of 8.7%, and is expected to grow to US$25.3 billion in 2025 at a CAGR of 1.5% from 2021 to 2025, and further grow to US$26.6 billion in 2030 at a CAGR of 1.0% from 2025 to 2030. The chart below illustrates the historical and forecasted global adalimumab market for the periods indicated:

Global Adalimumab Market, 2015-2030E

Period	Originator	Biosimilars	Total
2015-2021	6.7%	/	8.7%
2021-2025E	-11.0%	46.6%	1.5%
2025E-2030E	-4.6%	6.1%	1.0%

(US$ in billions)



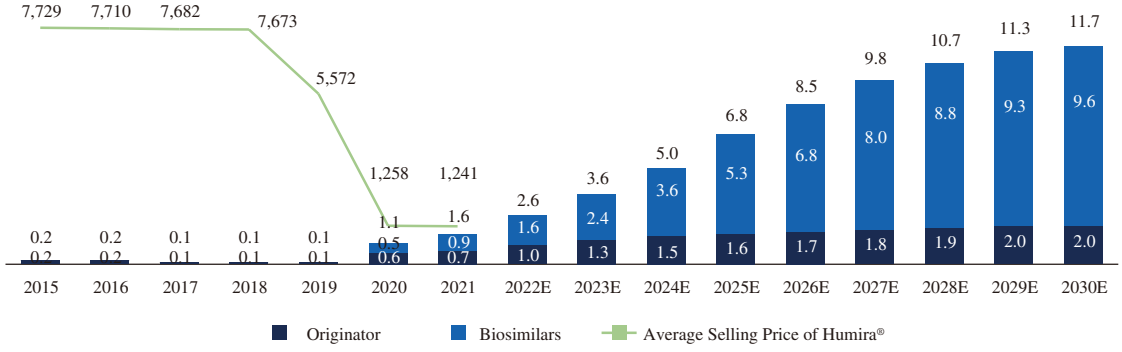
Source: Public disclosure of listed companies, expert interviews, Frost & Sullivan Analysis

Humira® was approved by the NMPA in 2010 and included in the National Reimbursement Drug List (NRDL) in 2019. Its average selling price was originally RMB7,729 per unit in 2015, and decreased from RMB5,572 in 2019 to RMB1,258 in 2020, directly contributing to a 440% increase in sales in 2020 compared to 2019.

Due to the wide range of indications for adalimumab, large market demand and continuous availability of new biosimilar products, the adalimumab market size is growing rapidly in China. In terms of sales revenue, the adalimumab market in China increased from RMB0.2 billion in 2015 to RMB1.6 billion in 2021 at a CAGR of 41.3%, and is expected to grow to RMB6.8 billion in 2025 at a CAGR of 42.7% from 2021 to 2025, and further grow to RMB11.7 billion in 2030 at a CAGR of 11.3% from 2025 to 2030. The chart below illustrates the historical and forecasted adalimumab market in China for the periods indicated:

Adalimumab Market in China, 2015-2030E

	Period	Originator CAGR	Biosimilars CAGR	Total CAGR
(Unit of Market Size: RMB in Billions)	2015-2021	23.1%	/	41.3%
(Unit of Average Selling Price: RMB)	2021-2025E	21.5%	54.3%	42.7%
	2025E-2030E	5.4%	12.8%	11.3%



Source: Public disclosure of listed companies, expert interviews, Frost & Sullivan Analysis

Growth Drivers of the Adalimumab Injection Market

Growth drivers of the adalimumab injection market include (i) improving regulatory landscape, (ii) expiration of the core patents of originator drugs and (iii) wide range of indications.

- *Improving regulatory landscape*. As biosimilars are not exact replicas of the originator drugs, the development of regulations governing the approval and market launch of biosimilars is a complex process. Health authorities around the world are working to establish clear regulatory pathways to ensure market access for qualified biosimilars. In 2006, the first biosimilar was approved for the European market. In March 2010, the U.S. government set out regulations of biosimilars for the first time in the Affordable Care Act. It was not until March 2015 that the first class of biosimilars was officially approved for the U.S. market via 315(k). Similar changes have been made in other countries and regions around the world, which has helped biosimilars enter the market.

- *Expiration of the core patents of originator drugs*. Patent protection for the antibody molecule of the originator (Humira®) expired in the U.S. in 2016, in China in 2017 and in the EU in 2018. The expiry of the aforementioned core patent protection for Humira® has enriched the competitive landscape of the adalimumab industry and provided opportunities for the development of a more affordable biosimilar market for adalimumab. According to the latest publicly disclosed price in February, 2023, the average price of adalimumab biosimilars (40mg) is RMB992/40mg, which is almost a quarter of the price of Humira

before it was covered by NRDL and RMB300 lower than Humira's price as of the Latest Practicable Date. Six Humira® biosimilars have been approved for marketing in China. In addition, Humira® was approved by the State Drug Administration of China in 2010 and included in the Class B list of the NRDL in 2019. Its price decreased from RMB5,572 in 2019 to RMB1,258 in 2020. The significant price reduction of Humira® is expected to stimulate potential clinical demand that has been suppressed due to high healthcare costs. With increased medical insurance coverage, patients' ability to pay will also be greatly enhanced, which will provide strong support for the development of biosimilars in China and accelerate the pace of market release.

- *Wide range of indications*. In December 2002, the U.S. Food and Drug Administration approved Humira® for the treatment of rheumatoid arthritis and subsequently approved indications including psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, septic sweat gland inflammation and juvenile idiopathic arthritis. In 2020, the number of approved indications for Humira® expanded to 17 worldwide. Most of these are chronic conditions require long-term regular treatment. In February 2010, the State Drug Administration of China first approved Humira® for the treatment of rheumatoid arthritis, and to date, eight indications have been approved in China, including rheumatoid arthritis, ankylosing spondylitis, psoriasis and uveitis.

Competitive Landscape

In 2021, Humira® recorded sales revenue of US$21.2 billion globally. The following table sets forth details of the global adalimumab injection market in terms of sales revenue in 2021:

Market Share of Global Adalimumab Market, 2021

Company Name	Product	Sales Revenue in 2021 (US$ million)	Market Share in 2021 (%)
AbbVie	Humira®	20,694.0	86.9%
Eisai	Humira®	552.9	2.3%
Amgen Inc.	Amgevita®	439.0	1.8%
Biogen Inc.	Imraldi®	233.0	1.0%
Others	/	1,896.0	8.0%

Notes:

(1) In February 2007, Eisai and Abbott announced an amendment to their agreement to co-market Humira® in Taiwan and Korea, with sales credited to Eisai's subsidiaries in Taiwan and Korea.

(2) In January 2008, Eisai and Abbott began to co-market the Humira® brand in Japan, using one brand, one channel and two promotional programs.

(3) In Europe and the U.S., adalimumab is exclusively distributed by Abbott (later spun off as AbbVie). In Korea and Taiwan, Eisai and Abbott jointly promote and distribute Humira® using a similar program to that in Japan.

In China, the high selling price of Humira® when it entered the market and the lack of education in autoimmune diseases led to low penetration and a declining sales trend from 2013 to 2019. With the inclusion of Humira® in the NRDL, Humira® sales increased significantly in the adalimumab injection market in China in 2020. The following chart and table set forth details of the adalimumab injection market in China in terms of sales revenue and market share in 2021:

Company Name	Product	Sales Revenue in 2021 (million RMB)	Market Share in 2021 (%)
AbbVie Inc.	Humira®	720.0	43.6%
Hisun Pharmaceutical (海正藥業)	Anjianning (安建寧)	450.0	27.3%
Bio-Thera Solutions, Ltd. (百奧泰)	QLETLI®/格樂立	306.3	18.6%
Innovent Bio (信達生物)	SULINNO® /蘇立信	110.0	6.7%
Henlius Biotech (復宏漢霖)	Handayuan (漢達遠)	62.5	3.8%

Note: Henlius Biotech (復宏漢霖) signed a cooperation agreement with Fosun Pharmaceutical (復星醫藥) regarding Handayuan (漢達遠). In 2021, Henlius Biotech received a profit share of RMB21.8 million from Handayuan under the cooperation agreement, and the sales revenue of Handayuan in 2021 is estimated to be RMB62.5 million with reference to the profit of similar products, as verified by expert interviews.

Source: Public disclosure of listed companies, expert interviews, Frost & Sullivan Analysis

As of the Latest Practicable Date, there were six Humira® biosimilar drugs approved and ten Humira® biosimilar drugs under development in China. The following tables set forth details of the Humira® biosimilars approved and under development in China:

Approved Products in China

Company Name	Product	NMPA Approval Date	Indications	Price
Bio-Thera Solutions, Ltd. (百奧泰)	QLETLI®/格樂立	November 6, 2019	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, uveitis, childhood plaque psoriasis, polyarticular juvenile idiopathic arthritis, Crohn's disease in children	RMB1,080/40mg RMB676/20mg
Hisun Pharmaceutical (海正藥業)	Anjianning (安建寧)	December 6, 2019	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, non-infectious uveitis, polyarticular juvenile idiopathic arthritis, childhood plaque psoriasis	RMB1,090/40mg
Innovent Bio (信達生物)	SULINNO®/蘇立信	September 2, 2020	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, polyarticular juvenile idiopathic arthritis, childhood plaque psoriasis, non-infectious uveitis	RMB1,088/40mg
Henlius Biotech (復宏漢霖)	Handayuan (漢達遠)	December 2, 2020	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, uveitis	RMB899/40mg
Chia Tai Tianqing (正大天晴)	Taibowei (泰博維)	January 18, 2022	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	RMB799/40mg
Junshi Biosciences (君實生物)/ Mabwell (邁威生物)	Junmaikang (君邁康)	March 1, 2022	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	RMB998/40mg

Source: CDE, public disclosure of listed companies, Frost & Sullivan Analysis

Products Under Development in China

Company Name	Products	R&D Progress	Indication	Date of Phase I Clinical Trial*
SinoCellTech (神州細胞)	SCT630	Phase III completed, pending approval	Moderate-to-severe plaque psoriasis	January 29, 2019
Wuhan Institute of Biological Products (武漢生物製品研究所)	Recombinant fully human anti-human TNF-α monoclonal antibody injection	Phase III	Moderate-to-severe plaque psoriasis	May 24, 2019
Shandong Danhong Pharmaceutical Co., Ltd (山東丹紅)	BC002	Phase III	Ankylosing spondylitis	April 25, 2019
Huaota Biopharm (華奧泰生物)	HOT-3010	Phase III	Moderate-to-severe plaque psoriasis	September 21, 2018
Hualan Bio (華蘭生物)	HL01	Phase III	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	May 21, 2018
Tonghua Dongbao Pharmaceutical (通化東寶)	DB101	Phase III	Moderate-to-severe plaque psoriasis	August 18, 2017
Luzhu Biotech (綠竹生物)	K3	Phase I (completed)	Rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis	November 13, 2018
Eastern Biotech (北京東方百泰生物/北京精益泰翔)	JY026	Phase I (completed)	Rheumatoid arthritis, ankylosing spondylitis	October 29, 2019
Anhui Weiming Damu Biomedicine Co., Ltd. (安徽未名達木生物醫藥有限公司)	Recombinant anti-TNF-α fully human monoclonal antibody injection	Phase I	Rheumatoid arthritis, ankylosing spondylitis	July 5, 2021
North China Pharmaceutical Company Ltd. (華北製藥)	Recombinant human anti-human tumour necrosis factor (TNF-α) monoclonal antibody injection	Phase I	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	January 15, 2020

Note:

* Date when the Phase I clinical trial was first published by the CDE.

Source: CDE, public disclosure of listed companies, Frost & Sullivan Analysis

RELAPSED OR REFRACTORY B CELL NON-HODGKIN LYMPHOMAS (NHL)/ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TREATMENT MARKET

Overview

B cell malignancies originate from different stages of B cell differentiation and constitute a heterogeneous group of cancers, including B cell lymphoma, B cell leukemia and plasma cell malignancy. B cell type non-Hodgkin lymphoma ("**NHL**") and B cell type acute lymphoblastic leukemia ("**ALL**") are the most common B cell malignancy.

NHL

Lymphomas are malignant neoplasms that originate in the lymphopoietic system and are the most common hematologic neoplasms worldwide. NHL is the most common type of lymphoma, accounting for 90% of newly diagnosed cases of lymphoma. There are several subtypes of non-Hodgkin's lymphoma, which are identified on the basis of their phenotype, surface proteins and genetic characteristics.

The number of new cases of NHL in China increased from approximately 81,000 in 2015 to 95,000 in 2021 at a CAGR of 2.6%, and is expected to increase to 104,000 in 2025 at a CAGR of 2.4% from 2021 to 2025, and further increase to 116,000 in 2030 at a CAGR of 2.1% from 2025 to 2030. The global number of new cases NHL increased from approximately 475,000 in 2015 to 546,000 in 2021 at a CAGR of 2.3%, and is expected to increase to 599,000 in 2025 at a CAGR of 2.3% from 2021 to 2025, and further increase to 669,000 in 2030 at a CAGR of 2.2% from 2025 to 2030.

ALL

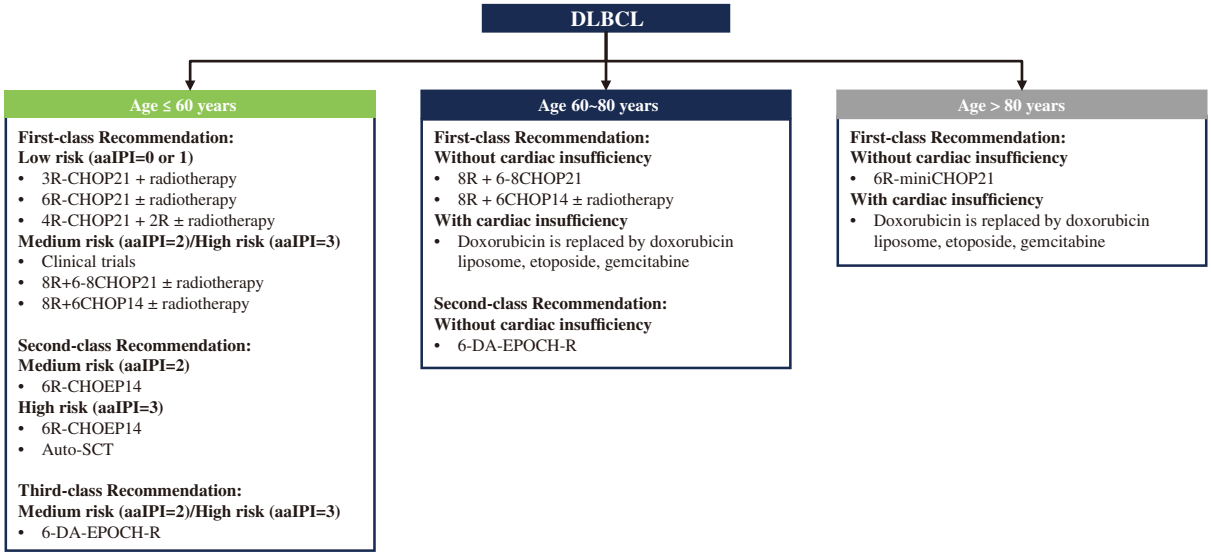
ALL is a heterogeneous hematologic malignancy that can develop in people of different ages groups, of which 80% of ALL cases occur in children. ALL is divided into two main categories, B-lymphocytic leukemia (B-ALL) and T-lymphocytic leukemia (T-ALL). In adults, approximately 75% of ALL cases are B-ALL and the rest are T-ALL.

The number of new cases of ALL in China increased from approximately 11,800 in 2015 to 13,000 in 2021 at a CAGR of 1.6%, and is expected to increase to 13,800 in 2025 at a CAGR of 1.5% from 2021 to 2025, and further increase to 14,700 in 2030 at a CAGR of 1.3% from 2025 to 2030. The global number of new cases NHL increased from approximately 62,200 in 2015 to 68,800 in 2021 at a CAGR of 1.7%, and is expected to increase to 73,300 in 2025 at a CAGR of 1.6% from 2021 to 2025, and further increase to 79,000 in 2030 at a CAGR of 1.5% from 2025 to 2030.

Relapsed or Refractory B cell NHL/ALL Treatment Modalities

Approximately 50% of those with NHL type B are relapsed-refractory, and approximately 15% of those with ALL type B are relapsed-refractory. The following table sets forth details of the treatment paradigm of B-NHL in China.

Treatment Paradigm of B-NHL in China (with DLBCL as an Example)

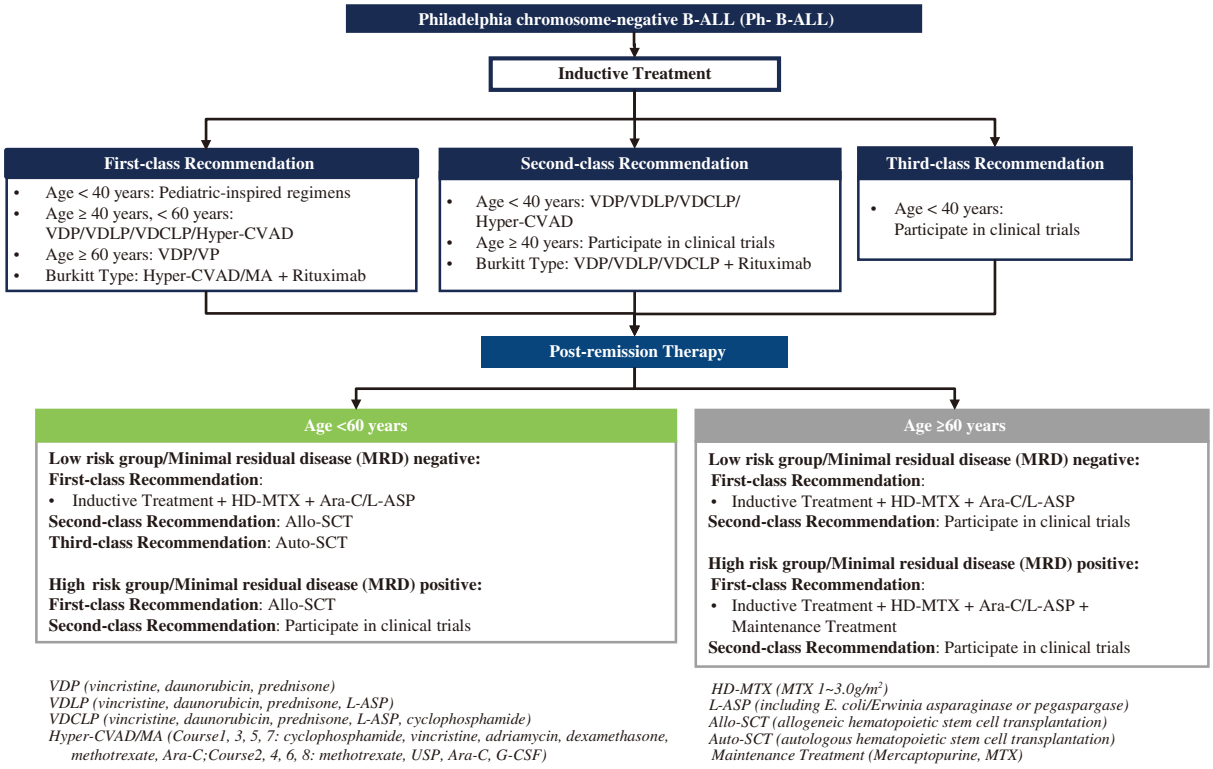


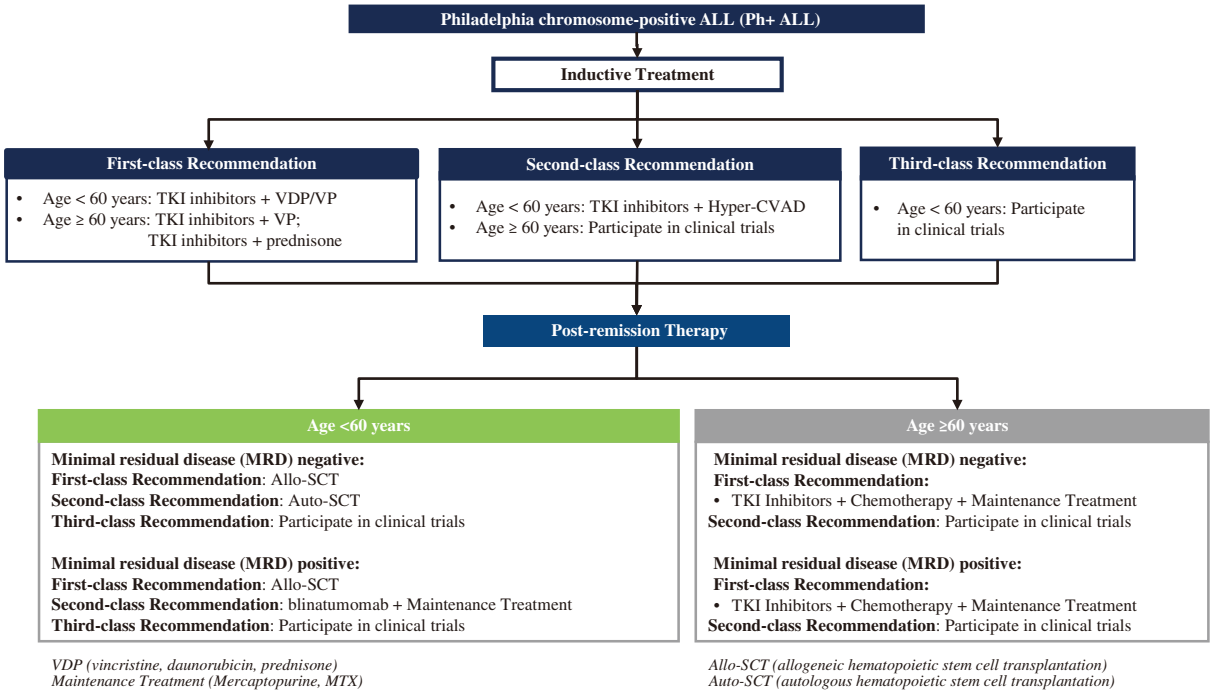
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

Source: 《2021CSCO淋巴瘤診療指南》, Frost & Sullivan Analysis

The following table sets forth details of the treatment paradigm of B-ALL in China.

Treatment Paradigm of B-ALL in China

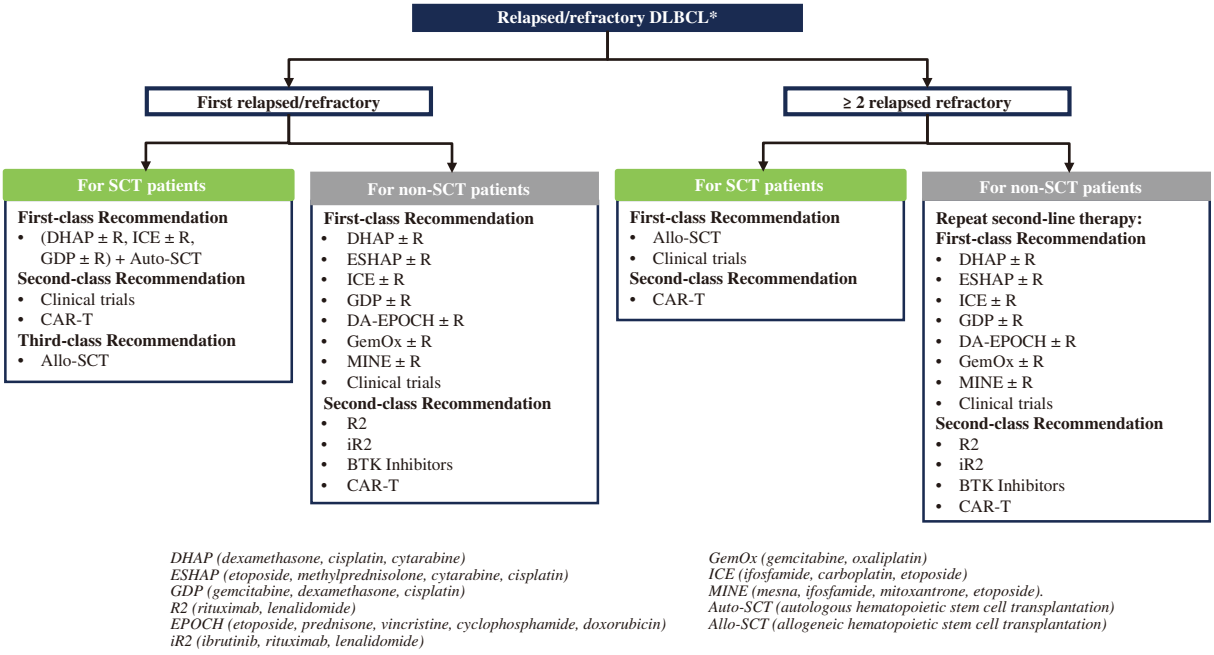




Source: 《2021CSCO恶性血液病診療指南》, Frost & Sullivan Analysis

The following table sets forth details of the treatment paradigm of relapsed/refractory B-NHL in China.

Treatment Paradigm of Relapsed/Refractory B-NHL in China (with DLBCL as an Example)



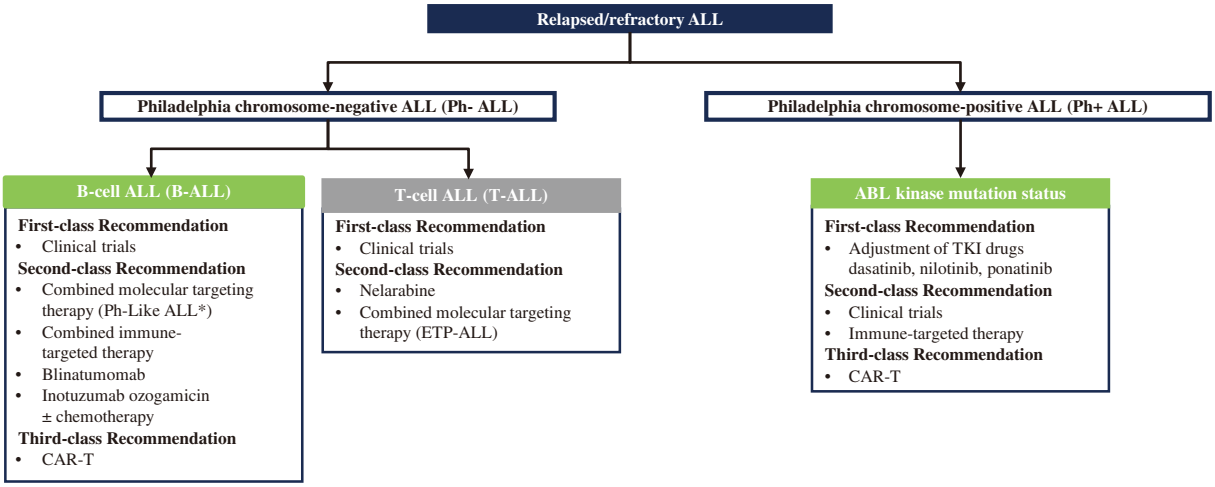
Note:

* *Appliable for patients receiving adequate doses of rituximab and anthraquinone-based chemotherapy during first-line therapy.*

Source: 《2021CSCO淋巴瘤診療指南》, Frost & Sullivan Analysis

The following table sets forth details of the treatment paradigm of relapsed/refractory ALL in China.

Treatment Paradigm of Relapsed/Refractory ALL in China



Note:

* *Detection of mutations with abnormal molecular biology in Ph-like ALL, ETP-ALL may benefit from combining molecularly targeted drugs.*

Source: 《2021CSCO惡性血液病診療指南》, Frost & Sullivan Analysis

Currently, the main treatment modalities for relapsed or refractory B cell NHL and B cell ALL are CD3/CD19 bispecific antibodies, anti-CD19 antibody drug conjugate (ADC), chimeric antigen receptor (CAR) T-cell therapy, and hematopoietic stem cell transplantation. The following table sets forth details of the immunotherapy modalities for relapsed or refractory B cell NHL and B cell ALL:

Drug	Mechanism of actions	Advantage	Disadvantage	Representative Drug/Fees	First to Market	Treatment duration	Dosage
CD19-CD3 Bispecific Antibodies	The CD19-CD3 bispecific antibody can bind to CD19 expressed on the surface of B cells at one end and to CD3 expressed on the surface of T cells at the other end. By linking CD19 malignant B lymphocytes to CD3+ T lymphocytes, the CD19-CD3 bispecific antibody mediates the lysis of tumor cells by T cells.	• Compared to single-antibody conjugation, bispecific antibodies have potential ease of drug combination, higher potential safety and better potential efficacy	• Weak market performance and clinical data of previous anti-tumor dual antibodies	Blincyto®/ US$178,000	2014	Each treatment includes (a) up to two cycles of a 42-day induction treatment, (b) up to three cycles of a 42-day consolidation treatment, and followed by (c) up to four cycles of a 84-day continued treatment	For individuals weighing 45kg or more First induction treatment: Day 1-7: 9 μg/d, Day 8-28: 9 μg/d, Day 29-42: no drugs provided during this period Second induction treatment: Day 1-28: 28 μg/d, Day 29-42: no drugs provided during this period Consolidation treatment: Day 1-28: 28 μg/d, Day 29-42: no drugs provided during this period Continued treatment: Day 1-28: 28 μg/d, Day 29-84: no drugs provided during this period For individuals weighing under 45kg, dosage is based on the individual's body surface area
Anti-CD19 ADCs	Made from a humanized anti-human CD19 monoclonal antibody coupled to a pyrrolobenzodiazepine (PBD) dimeric cytotoxin via Linker. Once bound to CD19-expressing cells, Zynlonta® is internalized by the cells and subsequently releases a cytotoxin that irreversibly binds to DNA, resulting in strong interstrand crosslinks that prevent DNA strand separation, thereby disrupting essential DNA metabolic processes such as replication and ultimately leading to cell death.	• Compared to single antibody drugs, ADC drugs have better early therapeutic efficacy, greater resistance to drug resistance, and greater clinical potential	• Overall technical complexity and high requirements for production technology	Zynlonta® (entering Phase I clinical trial in China)/ US$235,000	2021	Intravenous infusion administered over 30 minutes on day 1 of each cycle (every 3 weeks)	0.15 mg per kg of body weight every 3 weeks for 2 cycles 0.075 mg per kg of body weight every 3 weeks for subsequent cycles
CAR-T-cell Therapy	CAR-T cell technology is a T cell-based cellular immunology technology where T cells are genetically edited to incorporate chimeric antigen receptors to form CAR-T cells that can effectively capture and kill tumor cells to achieve therapeutic results.	• Good efficacy and high remission rate • May provide patients with long-lasting anti-tumor mechanisms	• Technology not yet mature, CRS side effects need to be addressed • Difficult to mass produce, high price	Yescarta®/ RMB1.2 Million	2017	Subject to doctor's evaluations, generally one to two treatments and each treatment lasts for two weeks	A suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL
Hematopoietic Stem Cell Transplantation	Hematopoietic stem cell transplantation is a process whereby hematopoietic stem cells from the donor are removed from the body as a graft and then transfused back to the pre-treated recipient to rebuild the recipient's hematopoietic and immune systems. Pre-treatment with ultra-lethal doses of chemoradiotherapy has a bone marrow-clearing effect and the graft has anti-leukemic and anti-tumor effects.	• Main treatment modality for many years in the past, clinically mature • Relatively low cost of treatment • Good postoperative results	• Mating restrictions • Graft-versus-host disease • Severe complications	–*/RMB300,000	–	Median treatment duration: four months	Peripheral blood mononuclear cells: 3 to 5 $\times10^8$ per kg of body weight, with peripheral blood CD34+ cells $\geq 2 \times10^6$ cells per kg of body weight, or bone marrow nucleated cells: 1 to 3 $\times10^8$ per kg of body weight, with bone marrow CD34+ cells equal to 1 to 2 $\times10^6$ cells per kg of body weight

Note:

* *Since hematopoietic stem cell transplantation refers to a process, no representative drugs are applicable.*

Source: Chinese Society of Clinical Oncology (CSCO), Frost & Sullivan Analysis

The following table sets forth the total fees for each treatment:

Drug	Representative drug	Per dose price	Total fees
CD19-CD3 Bispecific Antibodies	Blincyto®	RMB12,900/dose[(1)]	~US$178,000/course[(3)]
Anti-CD19 ADCs	Zynlonta®	US$25,415/injection[(2)]	~US$235,000/year[(4)]
CAR-T-cell Therapy	Yescarta®	RMB1.2 million/injection	~RMB1.2 million[(5)]

Notes:

(1) RMB12,900/dose is the bidding price of Blincyto®.

(2) US$25,415/injection is the price of Zynlonta® in the United States.

(3) For Blincyto®, the doctor will give a personalized treatment based on comprehensive diagnosis and analysis of the patient's condition. According to the instructions of Blincyto®, a course of treatment includes at most 2 cycles of induction therapy, 3 cycles of consolidation therapy and at most 4 cycles of maintenance therapy.

(4) For Zynlonta®, patients receive treatment until progressive disease or unacceptable toxicity.

(5) For Yescarta®, The frequency of treatment is subject to the the doctor's evaluation (generally 1-2 times in total).

CD19 has advantages which make it an important therapeutic target for relapsed-refractory B cell malignancies, including high expression on the surface of B cells and low expression on the surface of other cells, CD19 is not lost during the malignant transformation of B cells and remains effective in refractory/relapsed cases, and B cells can be effectively replenished after treatment is stopped.

Bispecific Antibodies

A bispecific antibody is an artificial protein that recognizes and specifically binds two antigens or epitopes. It simultaneously blocks the biological functions mediated by both antigens/epitopes or draws the cells of both antigens closer together and enhances the interaction. In recent years, a better understanding of the pathogenesis of various diseases and the rapid development of therapeutic monoclonal antibodies have also contributed to the development and advancement of bispecific antibodies. With the development of antibody construction, expression and purification techniques, dozens of structures have emerged from bispecific antibodies. The applications and research of existing bispecific antibodies are mainly focused on the field of oncology therapy.

CAR T-cell Therapy

CAR T-cell therapy uses a delivery vehicle such as a lentivirus (LV) to transfer therapeutic gene sequences to the T cell genome, enabling the patient's T cells to specifically recognize and bind to tumor cells, and subsequently kill them by releasing factors such as perforin. The therapy also results in the formation of memory T cells, providing patients with a long-lasting mechanism to fight tumors, effectively extending their survival rate and possibly even achieving a cure. Clinically, CAR T-cell therapy has shown significant efficacy in leukemia and non-Hodgkin's lymphoma.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is a process in which donor hematopoietic stem cells are removed from the body as a graft and then returned to the pre-treated recipient for transplantation to rebuild the recipient's hematopoietic and immune systems. Pre-treatment with super lethal doses of chemoradiotherapy has a bone marrow scavenging effect and the graft has an anti-leukemic (graft versus leukemia, GVL) and anti-tumor (graft versus tumor, GVT) effect and is used clinically to treat hematologic disorders and certain malignant solid tumors associated with hematopoietic stem cells.

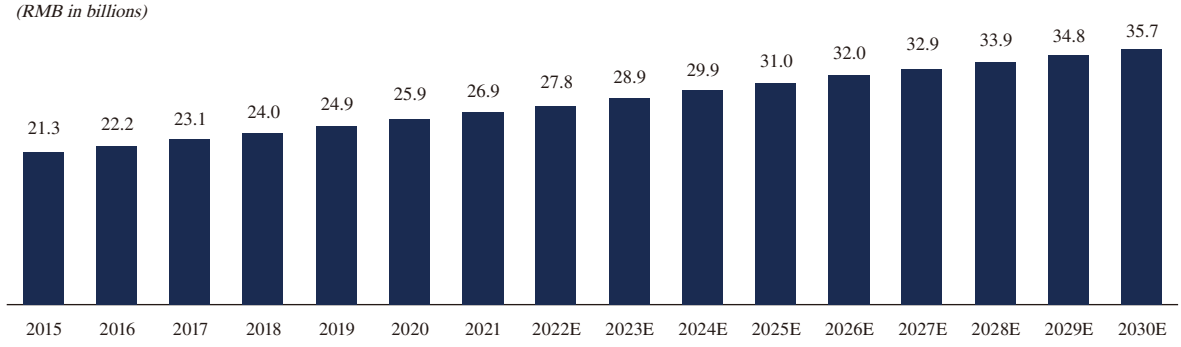
Market for Relapsed or Refractory B cell NHL/ALL Treatment

The incidence of hematologic malignancies such as lymphoma, myeloma and leukemia is increasing yearly, and although the application of various new drugs and protocols has greatly improved clinical treatment outcomes, the challenge in refractory recurrent hematologic tumors remains prominent. In China, the number of new cases of NHL was 95,000 in 2021. The majority of clinical NHL is of the B-cell type, accounting for 70%~85% of the total. In China, the number of new cases of ALL was about 13,000 in 2021. ALL is divided into two main categories, B-lymphocytic leukaemia (B-ALL) and T-lymphocytic leukaemia (T-ALL). According to the 2019 China Lymphoma Patient Survival White Paper, the average cost of non-first-time treatment is approximately RMB300,000 higher than the average cost of first-time treatment.

The relapsed or refractory B cell NHL/ALL treatment market in China increased from RMB21.3 billion in 2015 to RMB26.9 billion in 2021 at a CAGR of 4.0%, and is expected to increase to RMB31.0 billion in 2025 at a CAGR of 3.7% from 2021 to 2025, and further increase to RMB35.7 billion in 2030 at a CAGR of 2.9% from 2025 to 2030. K193 is expected to be launched in the market in year 2028 and the number of end-users is expected to reach 6.4 thousand in 2034. The chart below illustrates the historical and forecasted relapsed or refractory B cell NHL/ALL treatment market in China for the periods indicated:

Relapsed or Refractory B cell NHL/ALL Treatment Market in China, 2015-2030E

Period	CAGR
2015-2021	4.0%
2021-2025E	3.7%
2025E-2030E	2.9%



Source: Frost & Sullivan Analysis

Growth Drivers of the Relapsed or Refractory B cell NHL/ALL Treatment Market

Growth drivers of the relapsed or refractory B cell NHL/ALL treatment market include (i) incurability of relapsed or refractory hematologic malignancies, (ii) limited treatment options, (iii) major flaws in treatment methods and (iv) favorable policies.

- *Incurability of relapsed or refractory hematologic malignancies*. Currently, there are poor treatment options for relapsed or refractory B cell NHL/ALL, which represent an area of significant unmet medical need. Patients with relapsed/refractory B-cell NHL/ALL are those who have failed first-line therapy and need to continue second-or third-line therapy. Although conventional first-line treatments are proved to be beneficial, the five-year survival rates do not exceed 70%, whereas, simultaneously, almost half of the patients become resistant to or experience a relapse following treatment. For second-line treatment of NHL, there is a high degree of overlap between second-line and first-line treatment drugs in China, and in the area of end-line treatment, there are fewer drugs on the market, relying on stem cell transplantation. In addition, high-dose chemotherapy and autologous hematopoietic stem cell transplantation (Auto-HCT) offer a chance of cure for chemotherapy-sensitive patients with R/R DLBCL. However, only 50% of patients with R/R DLBCL are usually suitable for HCT treatment due to their advanced age and the presence of comorbidities. Patients with recurrent or refractory acute ALL have a poor prognosis, with less than 10% surviving 5 years. Related studies have shown that patients with Philadelphia chromosome-negative (Ph-) R/R ALL have poor survival outcomes, with a median overall survival (OS) of only 3.3 months and a 1-year OS rate of only 22%-24%. According to the *2021 CSCO Guidelines for the Diagnosis and Treatment of Lymphoma and* the *2021 CSCO Guidelines for the Diagnosis and Treatment of Hematological Malignancies,* there is no specific drug for patients with relapsed/refractory B-cell NHL/ALL. Grade I recommended treatment for relapsed/refractory B-cell NHL includes clinical trials of autologous hematopoietic stem cell transplantation and allogeneic hematopoietic stem cell transplantation. Patients who are ineligible for transplantation are encouraged to participate in clinical trials such as non-cross-resistant combination chemotherapy. Grade II recommended therapies include CAR-T therapy, BTK inhibitors combined with chemotherapy and radiotherapy. Patients who fail rescue therapy can also choose biological products for treatment, such as monoclonal antibodies. Patients are encouraged to participate in clinical trials. Treatment options include monoclonal immunotherapy targeting CD22 and CD19, CAR-T therapy targeting CD19 and CD22 in B-ALL, and hematopoietic stem cell transplantation. Current treatment options for relapsed/refractory B cell NHL/ALL are still in clinical trials. Autologous hematopoietic stem cell transplantation has been a major treatment for relapsed/refractory B-cell NHL/ALL for many years. It is clinically mature and the postoperative effect is good. However, transplant failure, recurrence after transplantation, or serious complications may still occur. Autologous hematopoietic stem cell transplantation was first launched in 1956, and its treatment cost is approximately RMB300,000. CAR-T cell technology is a cellular immune technology based on T cells. T cells add chimeric antigen receptors through gene editing to form CAR-T cells, which can effectively capture and kill tumor cells to achieve therapeutic effect. The marketed CAR-T therapy products in China include Yescarta® (launched by Fosun Kite in China in 2021, targeting CD19 and priced at RMB1.2 million per injection and Carteyva® (launched by JW Therapeutics in China in 2021, targeting CD19 and priced at RMB1.3 million per injection). In addition, other globally marketed CAR-T

products include Novartis' Kymriah, Gilead's Tecartus, BMS's Breyanzi and Abecma, and Legendary Bio/Johnson & Johnson's Carvykti. Although CAR-T therapy products are effective, the technology is not yet mature, and CRS side effects need to be addressed. CAR-T therapy products are difficult to mass produce and less accessible to patients due to the high cost of treatment. CD19-CD3 bispecific antibody therapy is a prospective treatment. One end of the CD19-CD3 bispecific antibody can bind to CD19 expressed on the surface of B cells, and the other end can bind to CD3 expressed on the surface of T cells. By connecting CD19 malignant B lymphocytes with CD3+T lymphocytes, CD19-CD3 bispecific antibodies can mediate the lysis of T cells to tumor cells. The first commercialized bispecific antibody product in China is Amgen's Blincyto® (launched in China in 2021, targeting CD19×CD3 and priced at RMB12,900 per dose, and RMB361,200 per course). Compared with monoclonal combination therapies, bispecific antibody therapies have higher potential safety and better potential efficacy. Up to 50% of patients with diffuse large B cell lymphoma are difficult to cure with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone (R-CHOP) therapy or relapse after achieving complete remission with first-line therapy. Approximately 60% to 70% of patients do not respond to current second-line therapy after first-line treatment, and of those who do respond to second-line therapy, approximately 50% will eventually relapse. Patients with relapsed or refractory B cell NHL have poor prognosis, and no treatment options are available for NHL. Patients with relapsed or refractory acute ALL have a dismal prognosis with less than 10% of patients surviving 5 years. With NHL causing approximately 54,351 deaths in China in 2020, there remains a significant unmet medical need for patients who have relapsed or are refractory to cure after receiving available therapies.

- *Limited treatment options*. Due to limited choices of mechanisms of action, existing therapies are unable to provide effective treatment for patients with different relapsed or refractory diffuse large B cell lymphomas. For example, rituximab maintenance therapy has no significant effect on patients with relapsed or refractory diffuse large B cell lymphomas who have relapsed after autologous stem cell transplantation. Second-line treatment options other than chemotherapy are also extremely limited in China compared to the U.S. Therefore, second-line patients eligible for transplantation in China are more likely to be treated with stem cell transplantation than in the U.S.

- *Major flaws in treatment methods*. The diagnosis of hematologic malignancies is usually through bone marrow examination and imaging. Most patients will opt for chemotherapy, targeted drugs, immunotherapy and, for those with the right conditions, bone marrow transplantation. The main drawbacks of current therapies are reflected in low overall response rates, high recurrence rates, side effects, long treatment cycles and high prices. Due to the lack of key drugs, inadequate adjuvant therapies and low early diagnosis rates, the five-year survival rates for hematologic malignancies in China are low, with NHL and multiple myeloma having five-year survival rates of approximately 37% and 25% respectively, which are lower than the survival rates for the same indications in the U.S. Curable immunotherapies have the potential to increase the market for relapsed or refractory B cell NHL/ALL treatment and are in high demand.

- *Favorable policies.* Economic, social and legal factors will have a significant impact on growth of the relapsed or refractory B cell NHL/ALL treatment market, as the market is heavily influenced by price, drug safety and the regulatory environment. The PRC government is implementing favorable policies and regulations to facilitate the development of new therapies. Special review channels such as priority review are also enabling accelerated launch of anti-tumor drugs. Policies such as the expansion of medical insurance, zero tariff on imported anti-cancer drugs and the negotiation of anti-cancer drugs into medical insurance will reduce the cost of anti-cancer drugs, further increasing the accessibility of innovative oncology immunology drugs.

Competitive Landscape

As of the Latest Practicable Date, there were three marketed drugs in China for third-line treatment of relapsed or refractory B cell NHL/ALL, comprising one bispecific antibody and two CAR T-cell therapies. The following table sets forth details of the marketed drugs in China for third-line treatment of relapsed or refractory B cell NHL/ALL:

Bispecific Antibodies

Year	Product	Company	Indication	Target	Effectiveness	Safety	Price
2020	Blincyto®	Amgen	Adults r/r ALL	CD19 × CD3	ORR: 44%, CR: 34%, mDOR: 7.3 month	CRS:15% (≥grade 3: 7%) NT: 65%	US$178,000

CAR-T

Year	Product	Company	Indication	Target	Effectiveness	Safety	Price
2021	Yescarta®	Fosun Kite Biotechnology	Adult r/r DLBCL, Adult r/r FL	CD19	Best ORR: 82%, Best CR: 58%, CR at 2 years: 37%, 2-yr PFS: 39%, 2-yr OS: 51%	CRS:93% (≥grade 3: 13%) ICANS : 64% (≥grade 3: 28%)	~RMB1.2 million
2021	Carteyva®	JW Therapeutics	r/r LBCL, r/r FL	CD19	Best ORR: 76%, Best CR: 52%	CRS:48% (≥grade 3: 5%) NT:20% (≥grade 3: 5%)	~RMB1.3 million

Notes:

(1) DLBCL = diffuse large B cell lymphoma; LBCL = large B cell lymphoma; FL = follicular lymphoma.

(2) For Carteyva®, the treatment duration varies depending on the doctor's evaluations, and the recommended dosage is 100×10^6 CAR-T cells.

Source: Guangdong Medicine Exchange, Frost & Sullivan Analysis

As of the Latest Practicable Date, there were over 30 drugs under development in China for third-line treatment of relapsed or refractory B cell NHL/ALL.

As of the Latest Practicable Date, there was one marketed CD3/CD19 bispecific antibody in China for the treatment of relapsed or refractory B cell NHL/ALL, four CD3/CD19 bispecific antibodies and one CD3/CD19/CD20 trispecific antibody under development in China for the treatment of relapsed or refractory B cell NHL/ALL. The following chart sets forth details of CD3/CD19 bispecific antibodies and CD3/CD19/CD20 trispecific antibody that are marketed or under development in China for the treatment of relapsed or refractory B cell NHL/ALL:

Name of Drug	Company Name	Indication	Target	Clinical Progress	Date of Clinical Publication[1]
Blincyto®	Amgen	Relapsed or refractory diffuse large B cell lymphoma	CD19 × CD3	Listed	2014 FDA 2020 NMPA
A-319	Generon Biomed[2]	Refractory or relapsed B cell lymphoma	CD19 × CD3	Phase I	April 8, 2019
K193	Luzhu Biotech	Refractory/relapsed B cell non-Hodgkin's lymphoma	CD19 × CD3	Phase I	November 18, 2019
CN201	Curon Biopharma	r/r-B-NHL	CD19 × CD3	Phase I	January 11, 2021
LNF1904	Shandong Xinshidai Pharmaceutical Co., Ltd	Refractory/relapsed B cell malignant tumor	CD19 × CD3	Phase I	September 15, 2022
CMG1A46	BioRay Pharmaceutical Chimagen Biosciences	B cell NHL	CD19 × CD20 × CD3	Phase I	April 27, 2022

Notes:

(1) Date of clinical publication is defined as the date of first publication of information based on clinical progress.

(2) Generon Biomed has changed its name to Evive Biotech.

Source: Frost & Sullivan Analysis

MYELOID LEUKEMIA TREATMENT MARKET

Overview

Acute myeloid leukemia (AML) is a disorder characterized by a clonal proliferation derived from primitive hematopoietic stem cells or progenitor cells. Abnormal differentiation of myeloid cells results in a high level of immature malignant cells and fewer differentiated red blood cells, platelets and white blood cells. The disease occurs at all ages, but predominantly occurs in older people (>60 years of age). Symptoms may include fatigue, difficulty breathing, easy bruising and bleeding, and increased risk of infection. AML typically presents with a rapid onset of symptoms that are attributable to bone marrow failure and may be fatal within weeks or months when left untreated.

The number of new cases of AML in China increased from approximately 28,000 cases in 2015 to 30,000 cases in 2021 at a CAGR of 1.6%, and is expected to increase to 32,000 cases in 2025 at a CAGR of 1.5% from 2021 to 2025, and further increase to 34,000 cases in 2030 at a CAGR of 1.3% from 2025 to 2030. The global number of new cases of AML increased from approximately 115,600 in 2015 to 127,800 in 2021 at a CAGR of 1.7%, and is expected to increase to 136,200 in 2025 at a CAGR of 1.6% from 2021 to 2025, and further increase to 146,700 in 2030 at a CAGR of 1.5% from 2025 to 2030.

The main treatment for most types of AML is chemotherapy, sometimes along with a targeted therapy drug. This might be followed by a stem cell transplant. Surgery and radiation therapy are not major treatments for AML, but they may be used in special circumstances. Patients with AML have the lowest five-year survival rate of any leukemia type. The proportion of patients suitable for stem cell transplant is low in terms of current treatment, and most patients fail to respond to chemotherapy and progress to relapsed/refractory AML. Relapsed/Refractory AML is difficult to treat due to its inherent difficulty in achieving complete remission, multiple complications and short survival.

THE FROST & SULLIVAN REPORT

In connection with the [**REDACTED**], we commissioned Frost & Sullivan, an Independent Third Party, to prepare a report on the vaccine market, relapsed or refractory B cell NHL/ALL treatment market, adalimumab injectable market and myeloid leukemia treatment market in China and globally. Frost & Sullivan is an independent global market research and consulting company which was founded in 1961 and is based in the United States. Services provided by Frost & Sullivan include market assessments, competitive benchmarking and strategic and market planning for a variety of industries. We have agreed to pay a total of RMB0.9 million in fees for the preparation of the Frost & Sullivan Report. The payment of such amount was not contingent upon our successful [**REDACTED**] or on the results of the Frost & Sullivan Report. Except for the Frost & Sullivan Report, we did not commission any other industry report in connection with the [**REDACTED**]. We have included certain information from the Frost & Sullivan Report in this document because we believe such information facilitates an understanding of the market where we operate our businesses for potential investors. Frost & Sullivan prepared its report based on its in-house database, independent third-party reports and publicly available data from reputable industry organizations. Where necessary, Frost & Sullivan contacts companies operating in the industry to gather and synthesize information in relation to the market, prices and other relevant information. Frost & Sullivan has exercised due care in collecting and reviewing the information so collected and believes that the basic assumptions used in preparing the Frost & Sullivan Report, including those used to make future projections, are factual, correct and not misleading. Frost & Sullivan has independently analyzed the information, but the accuracy of the conclusions of its review largely relies on the accuracy of the information collected. The market projections in the commissioned report are based on the following key assumptions: (i) the overall social, economic and political environment in China and globally is expected to remain stable during the forecast period; (ii) the pharmaceutical industry is expected to maintain a robust growth over the next few years; and (iii) no extreme force majeure or industry regulation will dramatically or fundamentally affect the market. Frost & Sullivan research may be affected by the accuracy of these assumptions and the choice of these primary and secondary sources. Except as otherwise noted, all data and forecasts in this section come from the Frost & Sullivan Report.