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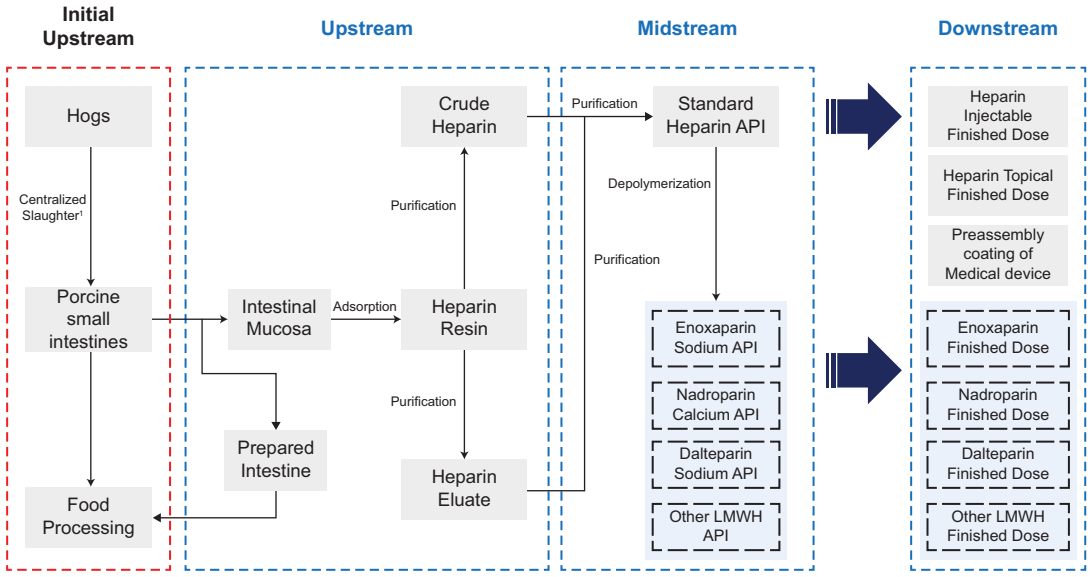
ENOXAPARIN FINISHED DOSE MARKET

Overview

Heparin Industry Value Chain

Heparin is a type of anticoagulant drug and heparin industry consists of the initial upstream procurement of porcine small intestines, the upstream purification of crude heparin, the midstream manufacture of heparin APIs and downstream manufacture and supply of heparin finished doses. The following flowchart illustrates the heparin industry value chain. The Group has an integrated business model covering the full heparin value chain.



1 Compared with US and EU, the centralization of slaughter in China is low.

Source: Frost & Sullivan Report

Characteristics

Enoxaparin is the gold standard treatment for various indications, including venous thromboembolism and pulmonary embolism, which generates huge market demands and demonstrates

significant market potential, according to the assessment report published by EMA in March 2017. Since it was first approved in 1987, enoxaparin finished dose has been marketed in over 100 countries, with millions of patients worldwide and billions of doses consumed, which enables it to become the largest LMWH player in the world. Enoxaparin is the authorized generic that is identical to Lovenox, a top selling drug in Sanofi's established drug portfolio.

Advantages

Compared with other major LMWH finished doses in the market such as dalteparin sodium and nadroparin calcium, enoxaparin sodium has superior pharmacological and chemical properties, including a longer elimination half-life, superior bioavailability and a higher anti Xa/IIa activity ratio. In addition, enoxaparin sodium is manufactured via ß-elimination and therefore does not bear the risk of nitrite impurity that can be carcinogenic and genetically toxic, while the manufacture process of dalteparin sodium and nadroparin calcium applies nitrous acid degradation that may result in nitrite impurity. Enoxaparin sodium also has a wider range of approved indications, as shown in the following table, more comprehensive delivery routes and better clinical performance. Therefore, enoxaparin finished dose is expected to replace other LMWH finished doses at a global scale.

LMWHs indications in China	Enoxaparin Sodium	Dalteparin Sodium	Nadroparin calcium
Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery			
Surgery	✓	✓	✓
Internal Medicine	✓	✗	✗
Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism	✓	✓	✓
Treatment of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction	✓	✓	✓
Extracorporal circulation in blood dialysis to prevent thrombosis	✓	✓	✓
Treatment of Acute ST-Segment Elevation Myocardial Infarction	✓	✗	✗

Source: Frost & Sullivan Report

Regulatory and Prescription Pathways

EU and the UK

In most of the EU countries, prescription of biosimilar enoxaparin sodium injection is based on brands, patients generally can only be given the same brand of enoxaparin finished doses as prescribed and different brands cannot be used interchangeably. In the UK, NHS guidelines do not allow automatic substitution of biosimilars at the pharmacy level. MHRA highly recommends that biologics, including biosimilars, shall be prescribed with their brand names. Such recommendation aims to ensure that these pharmaceutical products are not able to be substituted automatically at the pharmacy level. In Germany, products that are manufactured by the same supplier with the same production line are considered bio-identical regardless of the brand names. Only bio-identical biosimilars can be used interchangeably at the pharmacy level. Therefore, even belonging to the same active ingredient group, the originators and their biosimilars may not be considered interchangeable. To promote their products in the EU and the UK, enoxaparin suppliers need to proactively market their brand names to enhance their brand and product awareness among physicians in order for the physicians to prescribe more enoxaparin drugs of their brands.

China

In China, prescription of generic enoxaparin sodium injection has been based on brands. However, due to the Opinions issued by the State Council in April 2018, patients can be given enoxaparin finished doses with the same compound under different brands subject to patients' affordability and choices. On April 3, 2018, the State Council issued Opinions of the General Office of the State Council on the Reform and Improvement of Policies on the Supply, Security and Use of Generic Drugs (《國務院辦公廳關於改革完善仿製藥供應保障及使用政策的意見》 to promote the substitution of generic drugs. According to the Opinions, generic drugs sharing the same quality and efficacy as to the original drugs will be included in a list of drugs that can be used interchangeably with the original drugs. Except for special circumstances specified by the relevant authorities in China, prescription of enoxaparin shall be based on compounds. China has implemented the approval regime for generic drugs based on Quality Consistency Evaluation (QCE), which is expected to enhance the quality control of generic drug market in China and promote the generic drugs with high quality. If a generic drug passes QCE, it means the generic drug has demonstrated bioequivalence as to the originator drug which indicates the high quality of such generic drug. Doctors are generally more willing to prescribe the generic drug with the QCE qualification due to its proven quality consistency, which will drive up the sales volume of such generic drug. Therefore, to promote enoxaparin finished doses in China in the future, enoxaparin suppliers need to pass the QCE as the generic drugs without the QCE approval are expected to be gradually phased out in the future.

On March 29, 2019, CDE issued the 21st Catalog of Reference Finished Doses for Chemical Generics (《化學仿製藥參比製劑目錄（第二十一批） 》）, which for the first time covered enoxaparin finished doses under the Catalog of Reference Finished Doses for Chemical Generics （《化學仿製藥參比製劑目錄》）. This sets the foundation for enoxaparin finished doses to be approved based on QCE as only generic drugs covered by such catalog can be qualified for QCE approval. On October 15, 2019, NMPA issued the Technical Requirements for Evaluation of Quality and Efficacy Consistency of Chemical Generic Injections (Draft for comments) (《化學藥品注射劑仿製藥質量和療效一致性評價技術要求（徵求意見稿）》), indicating the commencement of establishing QCE approval regime for injectable generic drugs in China. On May 14, 2020, NMPA issued Notice of NMPA on the Implementation of the Quality and Efficacy Consistency Evaluation of Generic Chemical Injections（《國家藥監局關於開展化學藥品注射劑仿製藥品質和療效一致性評價工作的公告》）, which marked that QCE for generic chemical injections is officially implemented.

QCE approved generic drugs will also benefit from the Centralized Drug Procurement (CDP) scheme recently implemented in China. QCE approval is one of the requirements for generic drugs to participate in the CDP. CDP is a governmental nationwide pilot scheme, by which public health institutions are required to pre-set their drug procurement quantity and their procurement cycle, and purchase the drug at the price determined by open bidding. The bidding company with the lowest price offer for a specific drug will generally win the bid. Because of the intended quantity commitment for each bid-winning drug, the public healthcare institutions will procure the bid-winning drugs with priority and doctors will prescribe the drugs to meet the quantity commitment, which will significantly increase the sales volume of such drug and reduce the sales and marketing expenses of the pharmaceutical companies supplying such drugs. In December 2019, National Organization of Centralized Procurement and Use of Drugs Joint Procurement Office issued Documents on National Centralized *Drug Procurement* (*GY-YD2019-2*) (*《全國藥品集中採購文件 (GY-YD2019-2)》*), indicating the official start of the CDP in all the 31 provinces. As of the latest Practicable Date, 33 drugs were included in the CDP scheme, and most of them were generic drugs. In certain provinces

and cities in China, a generic drug with QCE qualification can directly join the CDP network without waiting for a new round of bidding cycle, which simplifies the participation and bidding process of CDP. For the generic drugs that have passed the QCE, they will enjoy the same treatment as the originator drugs during the CDP process, and are able to bid at the same price level as the originator drugs that is generally higher. In some province, such as Shanxi, generic drugs that passed QCE will be included in the list of drugs that can be substituted for the original drugs, and will be purchased preferentially for clinical use.

U.S.

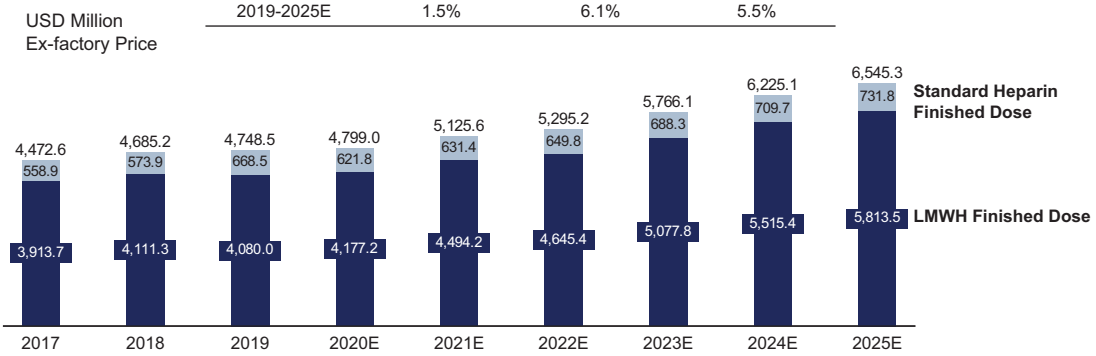
In the U.S., relying on the ANDA pathway, prescription of generic enoxaparin sodium injection is based on compounds, where enoxaparin finished doses with the same compound can be used interchangeably among different generic brands. In order to enhance their market shares, enoxaparin suppliers need to ensure their drugs are included in the purchase list of the Group Purchase Organizations (GPOs) in the U.S. as the GPOs currently dominate the distribution channel of generic drugs to the hospital market in the U.S. GPOs refer to the companies that help negotiate the prices of pharmaceutical products and services on behalf of healthcare providers, such as hospitals. GPOs represent some of the largest networks of hospitals and health care providers in the U.S. In 2019, more than 95% of hospitals in the U.S. belonged to a GPO, and about 73% of hospital purchases were via the GPO network. GPOs offer benefits to pharmaceutical manufacturers, as the GPOs can lower their sales and marketing costs and help them avoid duplicating those costs to promote their products among individual hospitals.

Market Size

The global heparin market comprises of heparin and low molecular weight heparin ("**LMWH**") finished doses. Enoxaparin is one type of LMWH. Due to wide clinical use, the global heparin market is expected to grow at a CAGR of 5.5% from US$4,748.5 million in 2019 to US$6,545.3 million by 2025. As clinical use of LMWH finished doses is generally safer with wider applications than that of heparin finished doses, LMWH finished doses have become the mainstream of heparin finished doses, accounting for more than 80% of the global heparin finished dose market by revenue in 2019, as shown in the following chart:

Global Market of Heparin Finished Dose by Sales Revenue (Ex-factory Price), 2017-2025E

CAGR	Standard Heparin Finished Dose	LMWH Finished Dose	Total
2017-2019	9.4%	2.1%	3.0%
2019-2025E	1.5%	6.1%	5.5%

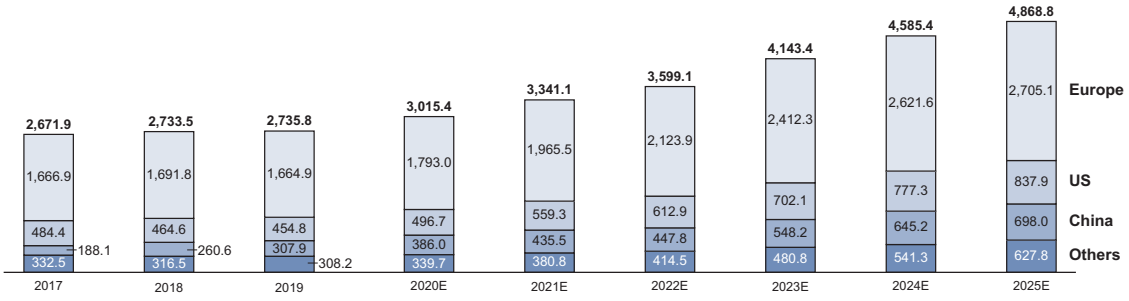


Source: Frost & Sullivan Report

Among the LMWH finished doses, enoxaparin finished dose has the largest proportion of the LMWH finished dose market. Enoxaparin finished dose has significant potential to replace other LMWH finished doses due to its wider indications and superior clinical effects, which will significantly stimulate the growth of global enoxaparin finished dose market. The enoxaparin finished dose accounted for 66.5% and 67.1% of the LMWH finished dose market by revenue in 2018 and 2019, respectively. It is expected that, by 2025, the enoxaparin finished dose will account for 83.7% of the LMWH finished dose market by revenue. Historically, due to market competition brought by generic drugs, revenue of global enoxaparin finished doses slightly increased from US$2,671.9 million in 2017 to US$2,735.8 million in 2019, representing a CAGR of 1.2%. The global usage of enoxaparin finished does reached 781.9 million syringe/vial in 2019, which is expected to reach 1,068.4 million syringe/vial in 2025. In particular, usage of enoxaparin in China is expected to increase at a CAGR of 23.6% from 52.0 million syringe/vial in 2019 to 185.5 million syringe/vial in 2025. Driven by the rapid expansion in China and the increasing price levels of the enoxaparin finished doses in the EU and the U.S., global market of enoxaparin finished dose is expected to grow at a CAGR of 10.1% and reach US$4,868.8 million in 2025. The charts below illustrate the global enoxaparin finished dose market size by region in terms of sales revenue:

Breakdown of Global Enoxaparin Finished Dose Market by Region in Terms of Sales, 2017-2025E

	CAGR	Europe	US	China	Others	Total
USD Million Ex-factory Price	2017-2019	-0.1%	-3.1%	27.9%	-3.7%	1.2%
	2019-2025E	8.4%	10.7%	14.6%	12.6%	10.1%



Source: Frost & Sullivan Report

Europe

Europe is the largest market of enoxaparin finished doses worldwide. Primarily due to market competition brought by generic drugs, the sales of enoxaparin finished doses in Europe historically declined from US$1,666.9 million in 2017 to US$1,664.9 million in 2019. However, driven by the price increase, European market is expected to reach US$2,705.1 million by 2025, representing a CAGR of 8.4% from 2019.

The Group is the leading enoxaparin finished dose manufacturer in the EU, accounting for 17.8% of market share by sales volume in 2019. The Group has the largest market shares in the UK and Poland, accounting for 60.3% and 52.6% of the UK and Poland markets in 2019, respectively. It also has leading market positions in Italy and Austria, with a market share of 34.7% and 19.1%, respectively in 2019. The following chart illustrates the market shares of the Group in the top seven EU enoxaparin finished dose markets in 2019, in total accounting for 17.8% of the market share by sales volume:

Country	2019 Enoxaparin Finished Doses Market Sales Volume (Million syringes/vials)	2019 Enoxaparin Finished Doses Sales Volume of the Company (Million syringes/vials)	Market Share of the Company by Sales Volume
Italy	79.0 (16.6%)[1]	27.5	34.7%
Germany	69.3 (14.6%)[1]	6.7	9.7%
France	54.9 (11.6%)[1]	3.1	5.6%
Spain	53.1 (11.2%)[1]	4.1	7.8%
Poland	45.0 (9.5%)[1]	23.7	52.6%
UK	27.0 (5.7%)[1]	16.3	60.3%
Austria	14.8 (3.1%)[1]	2.8	19.1%
Others	132.2 (27.7%)[1]	0.5	0.4%
Total EU	**475.3 (100.0%)[1]**	**84.6**	**17.8%**

1. % of total European Union market in 2019

Source: Frost & Sullivan Report

In Europe, the selling price of enoxaparin finished dose through pharmacy channel is generally more stable than the selling price through hospital channel, as the selling price through pharmacy channel is in general fluctuated less. For the enoxaparin finished dose, the selling price through pharmacy channel is typically higher than the price through hospital channel in many European countries. In some European countries, including UK, Germany and Poland, the pharmacy price is approximately two to three times higher than the hospital price, whereas in some other European countries, such as Spain, the price difference can be as high as five times. Therefore, more pharmaceutical companies are expected to directly sell their drugs through the pharmacy channel.

China

The enoxaparin finished doses market in China has grown rapidly in the recent years, increasing from US$188.1 million in 2017 to US$307.9 million in 2019 at a CAGR of 27.9%. The China market has significant growth potential. Compared with Europe and the U.S., in which the penetration rate of enoxaparin finished dose is relatively high, the usage per capita of enoxaparin finished dose in emerging market, such as China, is quite lower. Whereas the per capita use of enoxaparin in the EU was 0.95 dose in 2019, the per capita use remained relatively low in China, reaching 0.04 dose in 2019. Primarily driven by increasing clinical demand, the per capita use of enoxaparin in China is projected to grow to 0.31 dose in 2025. As more biosimilar enoxaparin finished dose products are marketed, and the awareness of the importance of anticoagulation in patients and doctors is increasing, the penetration rate of enoxaparin finished dose will keep increasing in emerging market, especially in China. Usage of enoxaparin in China was 52.0 million syringe/vial in 2019, which is expected to increase at a CAGR of 23.6% to 185.5 million syringe/vial in 2025. Total sales of enoxaparin in China reached US$307.9 million in 2019, representing a CAGR of 24.5% from 2014 to 2019, and is projected to reach US$698.0 million by 2025.

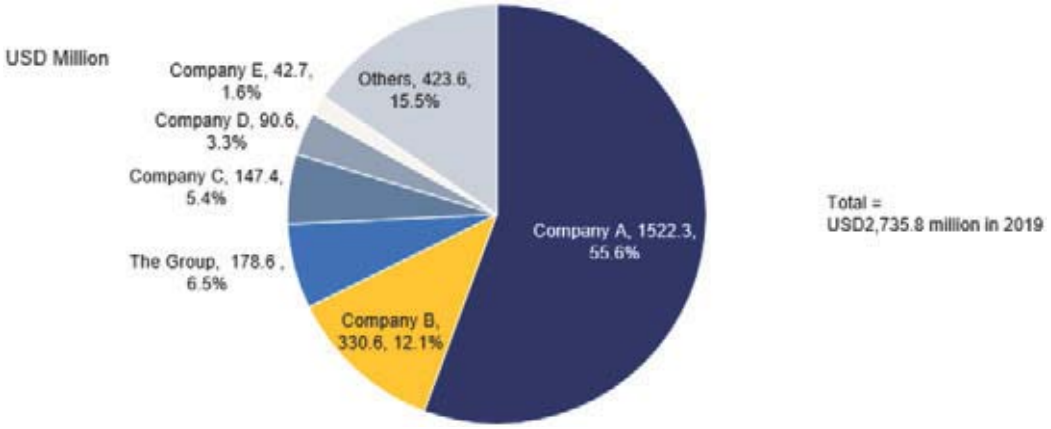
U.S.

In the U.S., primarily due to the introduction of generic drugs and Sandoz's suspension on the enoxaparin finished doses supply in July 2018, the sales of enoxaparin finished doses decreased from US$484.4 million in 2017 to US$454.8 million in 2019. However, the U.S. market is expected to recover and reach US$837.9 million in 2025 at a CAGR of 10.7% from 2019. In the U.S., the pharmacy price for the enoxaparin finished dose is about 30%-35% higher than the hospital price. The sales revenue from pharmacy channel and hospital channel accounted for 35% and 65% of the market share, respectively, in 2019. Companies who can supply their products through the pharmacy channel are able to acquire a higher profit margin.

Competitive Landscape

Global Competitive Landscape

The Group is the third largest supplier of enoxaparin finished dose globally, accounting for 6.5% of the global market by revenue in 2019. The following pie chart and table illustrate the global competitive landscape of enoxaparin finished dose suppliers in terms of market shares by revenue in 2019:



Source: Frost & Sullivan Report

Company	Market Share in 2019	Key Capacities and Differentiations
Company A	55.6%	Company A is a French multinational pharmaceutical company. It engages in the research and development, manufacturing and marketing of pharmaceutical drugs principally in the prescription market. Company A also develops over-the-counter medication. It covers seven major therapeutic areas: cardiovascular, central nervous system, diabetes, internal medicine, oncology, thrombosis and vaccines.
Company B	12.1%	Company B is a multinational pharmaceutical company with specialization in generic drugs. The other business areas include active pharmaceutical ingredients and proprietary pharmaceuticals.
The Group	6.5%	The Group is a leading China-based pharmaceutical company with global businesses in pharmaceutical, innovative biotech and CDMO sectors. It manufactures and sells anticoagulant and antithrombotic finished dose pharmaceutical products, including enoxaparin sodium injection and heparin sodium injection and their relevant APIs.
Company C	5.4%	Company C is a global healthcare company that specializes in medicines and technologies on infusion, transfusion and clinical nutrition. It offers a portfolio of injectable drugs and delivery systems used to treat a broad spectrum of patients, including oncology, anesthesia, analgesia, anti-infectives, parenteral nutrition, intravenous solutions and many other critical care therapies.
Company D	3.3%	Company D is a specialty pharmaceutical company, focusing on R&D, manufacture and commercialization of small molecule and specialty biologic drugs. Its services consist of contract manufacturing of aseptic filling, packaging of small-volume parenterals in prefilled syringes and vials, and provision of temperature-controlled storage facilities.
Company E	1.6%	Company E is a US-based pharmaceutical company. Its major product consists of enoxaparin sodium injection, cosyntropin for injection, hyaluronidase injection, medroxyprogesterone acetate injectable suspension and isoproterenol hydrochloride injection.

Source: Frost & Sullivan Report

The tables below set forth FDA approved enoxaparin sodium injections and EMA approved enoxaparin sodium injections via centralized procedure:

FDA Approved Enoxaparin Sodium Injections

Proprietary Name	Applicant Holder	FDA Approval Date	Drug Classification	Dosage Form	Retail Price(USD)[1]
Lovenox/ Clexane	Sanofi	1993	Originator	0.4ml: 4,000AXalU	39.4
Enoxaparin Sodium	Sandoz	2010	Generic	0.4ml: 4,000AXalU	12.8[2]
Enoxaparin Sodium	Amphastar	2011	Generic	0.4ml: 4,000AXalU	12.8[2]
Enoxaparin Sodium	Teva	2014	Generic	0.4ml: 4,000AXalU	12.8[2]
Enoxaparin Sodium	Apotex	2018	Generic	0.4ml: 4,000AXalU	12.8[2]
Enoxaparin Sodium	Nanjing King-Friend	2019	Generic	0.4ml: 4,000AXalU	N/A

1. Medium retail price for the dosage form of 0.4ml: 4,000AXalU per syringe in 2019
2. Average price of enoxaparin generic drugs
Source: FDA and Frost & Sullivan analysis

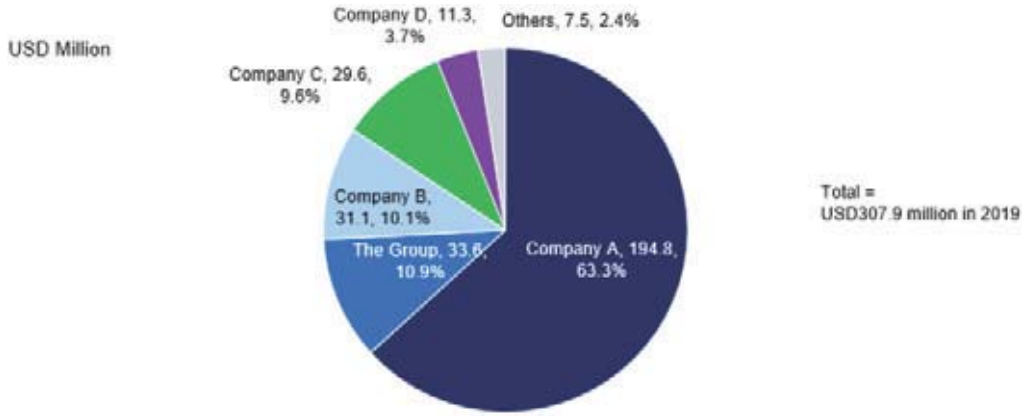
EMA Approved Enoxaparin Sodium Injections via Centralized Procedure (CP)

Proprietary Name	Applicant Holder	Approval Date	Region	Drug Classification
Inhixa	Techdow	2016	EU	Biosimilar

Note: Lovenox was approved in EU countries separately. Its first marketing approval was granted in France in 1987
Source: EMA and Frost & Sullivan analysis

Competitive Landscape in China

The Group is the first company that obtained NMPA approval to market enoxaparin generic drugs in China and the second largest supplier of enoxaparin in China with 10.9% market share by revenue in 2019. The following chart and table show the competitive landscape in China in terms of market shares by revenue in 2019:



Source: Frost & Sullivan Report

Company	Market Share in 2019	Key Capacities and Differentiations
Company A	63.3%	Company A is a French multinational pharmaceutical company. It engages in the research and development, manufacturing and marketing of pharmaceutical drugs principally in the prescription market. Company A also develops over-the-counter medication. It covers seven major therapeutic areas: cardiovascular, central nervous system, diabetes, internal medicine, oncology, thrombosis and vaccines.
The Group	10.9%	The Group is a leading China-based pharmaceutical company with global businesses in pharmaceutical, innovative biotech and CDMO sectors. It manufacture and sell anticoagulant and antithrombotic finished dose pharmaceutical products, including enoxaparin sodium injection and heparin sodium injection and their relevant APIs.
Company B	10.1%	Company B is a pharmaceutical enterprise specializing in R&D, manufacture and sales of gene engineering and biologics. Its products include rhG-CSF (filgrastim), enoxaparin sodium, interleukin-eleven (oprelvekin), palonosetron hydrochloride, rhBMP-2 (recombinant human Bone Morphogenetic Protein-2).
Company C	9.6%	Company C is a China-based company principally engaging in the research and development, production and sales of heparin-related products. Its major products include heparin API and low molecular weight heparin preparations, such as heparin sodium raw materials, heparin sodium, enoxaparin sodium injection, dalteparin sodium injection and nadroparin calcium injection. Company C mainly exports its heparin API to the United States and European countries.
Company D	3.7%	Company D is a China-based pharmaceutical company. Its products include ginkgolide injection, enoxaparin sodium, ambroxol hydrochloride, pantoprazole sodium, lansoprazole, clindamycin phosphate and azithromycin.

Source: Frost & Sullivan Report

The table below sets forth and compares the approved enoxaparin sodium injections in China:

Proprietary Name	Applicant Holder	NMPA Approval Date	Drug Classification	NRDL Status[1]	Dosage Form	Bidding price(RMB)[2]
Clexane	Sanofi	1997	Originator	2019 NRDL	0.4ml: 4,000AXaIU	51.5
Enoxaparin Sodium	Shenzhen Techdow Pharmaceutical (深圳市天道醫藥有限公司)	2005	Generic	2019 NRDL	0.4ml: 4,000AXaIU	39.3
Enoxaparin Sodium	Hangzhou China Gene Engineering (杭州九源基因工程有限公司)	2006	Generic	2019 NRDL	0.4ml: 4,000AXaIU	34.6
Enoxaparin Sodium	Nanjing King-Friend Biochemical Pharmaceutical (南京健友生化製藥股份有限公司)	2014	Generic	2019 NRDL	0.4ml: 4,000AXaIU	33.5
Enoxaparin Sodium	Suzhou Erye Pharmaceutical (蘇州二葉製藥有限公司)	2014	Generic	2019 NRDL	0.4ml: 4,000AXaIU	45.4
Enoxaparin Sodium	Baiyu Group (成都百裕製藥股份有限公司)	2015	Generic	2019 NRDL	0.6ml: 6000AxaIU	47.0
Enoxaparin Sodium	Changzhou Qianhong Bio-Pharma (常州千紅生化製藥股份有限公司)	2015	Generic	2019 NRDL	0.4ml: 4,000AXaIU	33.3
Enoxaparin Sodium	Beijing SL Pharmaceutical (北京雙鷺藥業股份有限公司)	2016	Generic	2019 NRDL	0.4ml: 4,000AXaIU	48.0
Enoxaparin Sodium	Dongying Tiandong Pharmaceutical (東營天東製藥有限公司)	2017	Generic	2019 NRDL	0.4ml: 4,000AXaIU	42.0
Enoxaparin Sodium	Hebei Changshan Biochemical Pharmaceutical (河北常山生化藥業股份有限公司)	2019	Generic	2019 NRDL	N/A	N/A

1. The version of NRDL by which the drug is covered
2. Medium published provincial bidding price per syringe in 2019
Source: Provincial Drug Centralized Procurement Platform, CDE and Frost & Sullivan analysis

Even though the generic drugs of enoxaparin in total account for 37.1% of enoxaparin sales in China, none of them has been approved based on QCE. To further regulate the enoxaparin market and strengthen quality control in China, the NMPA has implemented approval regime of injectable pharmaceuticals based on QCE in May 2020. It is expected that enoxaparin products that pass the QCE will gradually replace the low quality LMWH products due to the proven high quality of QCE-approved enoxaparin.

Before filing the application for QCE-approval with the NMPA for their enoxaparin products, pharmaceutical companies are required to first complete the bioequivalence test ("**BE test**"). As of the Latest Practicable Date, among the eight applicant holders of enoxaparin finished dose, three have already accomplished BE tests and filed for QCE-approval with NMPA, and the Group was the first company among the three. It is estimated that at least three market players will obtain the QCE approval in the upcoming two years.

Entry Barriers

Global Operation Capability

While Europe is the largest market of enoxaparin finished dose, raw materials are mainly sourced from China and enoxaparin API manufacturers for supplying to third parties are primarily based in China. Market players are, therefore, required to be able to operate at a global scale and engage in global sourcing, logistics and distribution arrangements. Companies with integrated business model covering multiple stages of the heparin value chain have competitive advantages in building

business relationships with multinational pharmaceutical companies. Lack of such global operation capability or integrated business model may become an entry barrier for new entrants.

Strict Quality Control

Since the Baxter Incident in 2008 and the outbreak of African swine fever in 2018, regulators have increasingly tightened the quality control requirements on heparin products. In order to accommodate such requirements, market players need to continuingly enhance their compliance with CGMP standards. It may be costly, time-consuming and challenging for new entrants to compete with established market players and meet such strict quality control requirements.

Limited Upstream Supply

Manufacturing of enoxaparin API is concentrated in China and therefore demand for heparin raw materials is high. Many enoxaparin manufacturers are expanding to upstream heparin value chain, such as processing of pig small intestines and manufacturing of crude heparin. The limited upstream supply has led to a stable competitive landscape for enoxaparin finished dose, where a few market players have established long-term exclusive cooperative relationships with the upstream suppliers. New entrants may find it difficult to secure sufficient raw material supply at reasonable price.

Growth Drivers and Future Trends

Growth Drivers

- *Increasing clinical demand*—Growth in aging population will result in a significant increase in the prevalence of chronic and cardiovascular diseases. It is estimated that the population over age 65 will increase at a CAGR of 2.6% from 665.7 million in 2018 to 774.9 million in 2024 globally, and such increase will drive the clinical demand for anticoagulants, especially enoxaparin finished dose products.
- *Growth of emerging markets*—With more marketing activities for enoxaparin finished dose products, the awareness of the importance of anticoagulation in patients and doctors will increase. The penetration rate of enoxaparin finished dose in emerging markets, especially, China, will continuingly increase, which will stimulate the further growth of global enoxaparin finished dose market.
- *Increase in pricing*—It is expected that the price of heparin APIs will increase significantly by 2020 and stay at the high level till 2024 due to the impact of the African swine fever in China. As the largest heparin APIs export country, the fluctuation in supply and price of heparin APIs in the China market will have a significant impact on the global market. The price increase of heparin APIs will ultimately be transferred to the price of downstream enoxaparin finished doses, which will promote the growth of the global enoxaparin finished dose market.

Future Trends

- *Indication and application expansion*—The clinical applications of enoxaparin finished dose are continuingly expanding. Studies have shown that enoxaparin finished dose is able to treat various diseases in the areas of cardiology, nephrology and neurology. Compared to novel oral anticoagulants (NOACs), enoxaparin finished dose has wider applications

and can be used for treatments in which the use of NOACs has not been approved. For example, enoxaparin finished dose can be used to treat acute ST-segment elevation myocardial infarction and prevent thrombosis in blood dialysis, and for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The wide application and continuous expansion of the indications of enoxaparin finished dose demonstrate significant growth potential of the global enoxaparin market.

- *Product upgrades*—There are a large number of unclassified LMWH finished doses in China with different manufacturing processes, low quality and lack of clinical data support for efficacy and safety. As an effort by the NMPA to tighten the drug quality control requirements, NMPA has implemented the QCE approval regime for injection doses in May 2020. Chinese Pharmacopeia Commission (CPC) is also refining the Chinese Pharmacopeia standards to regulate the market. With these initiatives by both NMPA and CPC, it is anticipated that an increasing number of unclassified low-quality LMWH finished dose products will be replaced by enoxaparin finished dose products due to the superior clinical effects and outstanding safety profile. Enoxaparin finished dose products are also expected to supplant heparin products in the EU, primarily resulted from their superior efficacy and stable anticoagulant effect.
- *Scaled purchases*—As the second largest pharmaceutical market globally, China's pharmaceutical market has significant growth potential. In addition to the expanding clinical applications of enoxaparin finished dose and its superior therapeutic effects on certain high-mortality diseases, the recent reforms in China's pharmaceutical policies, such as Centralized Drug Procurement, will also contribute to a growing enoxaparin finished dose market in China. Under the mechanism of Centralized Drug Procurement, enoxaparin finished dose may be purchased in large quantity, which enables the manufacturers to gain a significant market share with lower marketing expenses.

HEPARIN API MARKET

Overview

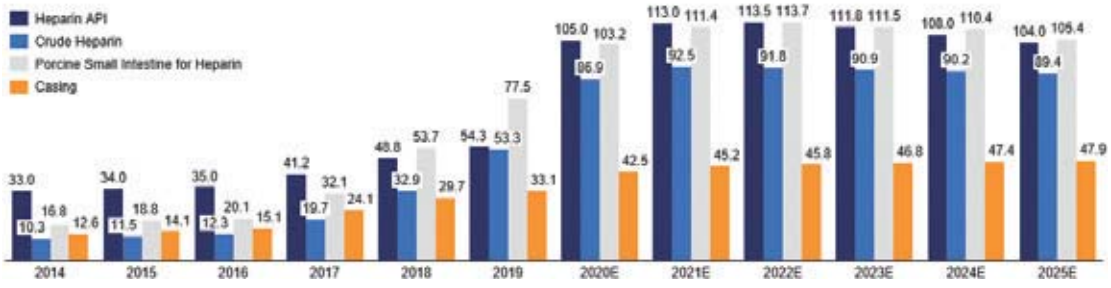
Heparin API is the active pharmaceutical ingredient and the raw material for manufacturing enoxaparin API and other LMWH APIs, which will be used for manufacturing enoxaparin finished doses and other LMWH finished doses. It is expected that pricing of heparin API will increase significantly in the future due to factors from both demand and supply sides. The global heparin API price is US$54.3 per mega in 2019, representing a CAGR of 10.5% during 2014 to 2019, and is expected to reach US$104.0 per mega in 2025 with a CAGR of 11.4%. Downstream of the heparin value chain, i.e. heparin finished dose and LMWH finished dose, are expected to continuingly expand due to clinical needs, which will generate additional demands for the heparin APIs, and push up both the sales volume and the price of the heparin API. Meanwhile, the upstream market, i.e. crude heparin, is heavily influenced by the supply of breeding stock pigs. The shortage of breeding stock pigs will result in a decreasing supply of porcine small intestines, one of the major raw materials for crude heparin. As there is no substitute of porcine small intestine as the raw material of enoxaparin and its derivatives, such decrease in the quantity of the porcine small intestines will lead to an increase in the price of porcine small intestines, which will be transferred downstream to the price of crude heparin, and further increase the price of heparin API. The shortage of upstream heparin raw materials may lead to insufficient supply of downstream products. As of the Latest Practicable Date, certain heparin finished doses were on the FDA drug shortages list, and had experienced periodic supply shortages in

the U.S. Due to the outbreak of the African swine fever, the United States House Committee on Energy and Commerce, in a letter issued in July 2019, alerted the FDA of the outbreak's potential threat to the U.S. heparin supply and advised the FDA to closely monitor the adequacy of the U.S. heparin supply. As the market demand for "gold standard" anticoagulant and antithrombotic drug remains strong, such shortage in heparin finish doses has created opportunities for market players with integrated business model covering upstream crude heparin supply and strong global sourcing capacities, such as the Group.

In China, three main factors have intensified the shortage of breeding stock pig supplies: (1) the cyclicity of hog price; (2) tightened environmental requirements; and (3) outbreak of African swine fever. First, breeding stock hogs generally have an industry price cycle of four to five years. The hog price uptrend generally lasts for about one to two years, whereas the hog price downtrend lasts for about two to three years. The hog price uptrend of the current cycle started in late 2018. It is expected that the hog price will reach the peak by 2020. Second, since 2017, the Chinese government has increasingly tightened the requirements on the environmental protection of pig breeding and many farms in China have been closed or relocated. Most importantly, the existing farms need to be equipped with pollution control facilities, which significantly increases the cost of pig breeding. Such cost increase is ultimately transferred to the prices of porcine small intestine and crude heparin, the effect of which is expected to continue in the long term. Third, due to the outbreak of African swine fever in late 2018, the number of breeding stock pigs had decreased constantly since the beginning of 2019, and continued throughout 2019, which led to the shortage in supply and a price increase in porcine small intestines, and therefore the shortage in supply and a price increase in crude heparin. As China has the largest heparin API output in the world, and the global demand for heparin API remains inelastic in 2019, such shortage in supply and increased price in crude heparin have resulted in a decrease in the sales quantity of heparin API and an increase in the price of heparin API. The porcine small intestine price increased by 44.3% from 2018 to 2019. Generally, there is one year lag from the price increase of porcine small intestine to that of heparin API. It is estimated that heparin API price will increase by 93.4% from 2019 to 2020. The following chart illustrates the price transmission from porcine small intestines to heparin API:

Global Heparin API Price and Forecast, 2014-2025E

USD/ Mega	CAGR	Heparin API	Crude Heparin	Porcine Small Intestine	Casing
	2014-2019	10.5%	38.9%	35.7%	21.3%
	2019-2025E	11.4%	9.0%	5.3%	6.4%



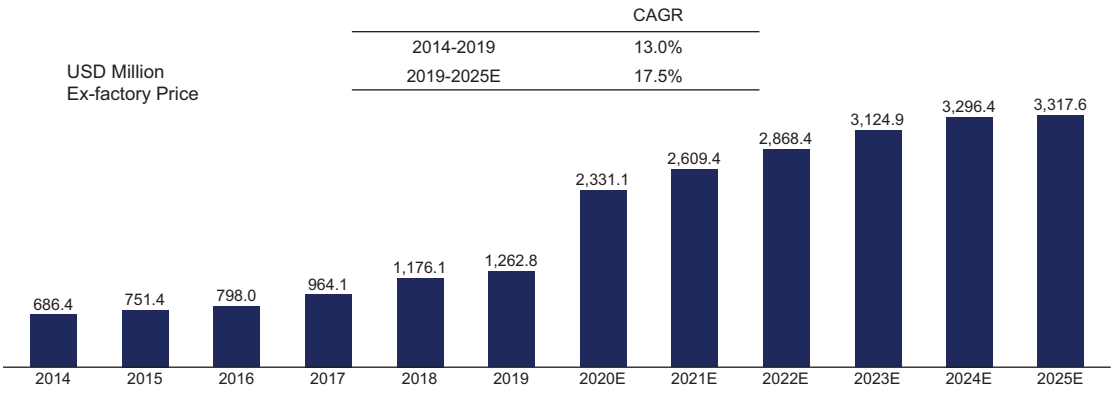
Source: Frost & Sullivan Report

Market Size

The global sales of heparin API increased steadily from US$686.4 million in 2014 to US$1,262.8 million in 2019, representing a CAGR of 13.0%. The situation changed in 2019 as a result

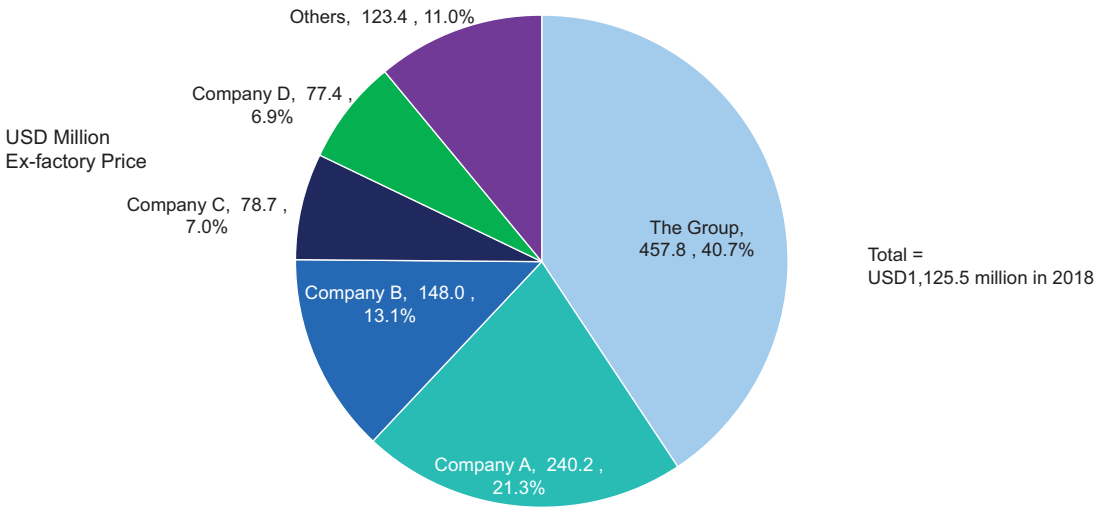
of the significant drop in the number of breeding stock pigs in China in 2019 due to the outbreak of African swine fever in late 2018, which caused the shortage and price increase of crude heparin. As a result, heparin API price is expected to increase significantly from 2019 to 2020 and stay at high level till 2025, which will drive the growth of global heparin API market. The global sales of heparin API is projected to reach US$3,317.6 million in 2025, representing a CAGR of 17.5%, as shown in the following chart:

Global Heparin API Sales Revenue by Ex-factory Price (Excluding Trading between Affiliates), 2014-2025E



Source: Frost & Sullivan Report

The global heparin API supply market is highly concentrated with the major suppliers based in China. The top five market players in total accounted for 89.0% of the market share in 2018, and four of them are based in China. The Group is the largest heparin API supplier globally with US$457.8 million sales accounting for 40.7% of the market share in 2018. The following chart and table illustrate the market size by sales revenue per market player in 2018 and the key capacities of the major market players:



Source: Frost & Sullivan Report

Company	Market Share in 2018	Key Capacities and Differentiations
The Group	40.7%	The Group is a leading China-based pharmaceutical company with global businesses in pharmaceutical, innovative biotech and CDMO sectors. It manufacture and sell anticoagulant and antithrombotic finished dose pharmaceutical products, including enoxaparin sodium injection and heparin sodium injection and their relevant APIs.
Company A	21.3%	Company A is a Spain-based life science company specializing in the identification, extraction and development of biomolecules of high biological and therapeutic value for the pharmaceutical and nutraceutical industries. Its products include heparin API and other animal-derived APIS and ingredients such as chondroitin sulfate, glucosamine, hyaluronic acid, native type II collagen or thyroid.
Company B	13.1%	Company B is a China-based company principally engaging in the research and development, production and sales of heparin-related products. Its major products include heparin API and low molecular weight heparin preparations, such as heparin sodium raw materials, heparin sodium, enoxaparin sodium injection, dalteparin sodium injection and nadroparin calcium injection. Company B mainly exports its heparin API to the United States and European countries.
Company C	7.0%	Company C primarily engaging in the research and development, manufacture and sales of bio-pharmaceutical products, mainly focusing on polysaccharides and enzymes. Its business scope ranges from lyophilized powder for injections (including antineoplastic drugs) and small volume parenteral solutions, to tablets, hard capsules, granules, and APIs.
Company D	6.9%	Company D is an enterprise group that combines pharmaceutical R&D, production, marketing, and capital operations across the fields of biochemical API, chemical synthetic drugs, and modern Chinese medicine.

Source: Frost & Sullivan Report

Future Trends

Increasing price level of crude heparin

The manufacture of heparin APIs heavily relies on the supply of porcine small intestine and is sensitive to environmental protection pressure. The impact of African swine fever in China is expected to last 3 to 5 years, and considering the growth cycle of hogs, it may take 4-6 years for the overall supply of hogs to recover. Therefore, the supply of crude heparin will be continuously limited. The supply of slaughtered hogs in China accounted for 53.4% of the global supply in 2018. Thus the price level of crude heparin will remain high in the short to medium term.

Industrial integration

Along with the strengthened quality control of heparin API and the tight supply of traceable heparin crude as raw materials, heparin API manufacturers are expected to ramp up their efforts in vertical industry value chain integration, in particular integration with the upstream supply of heparin raw material in order to ensure quality and quantity of raw materials and control production costs. As

the utilization rate of porcine small intestines is becoming saturated in China, heparin API manufacturers will seek raw material resources from other countries. Therefore, market players with integrated business model covering upstream crude heparin supply and strong global sourcing capacities are expected to enjoy significant competitive advantages to meet the growing market demand.

Steady growth of downstream LMWH finished doses

Due to the expanding indications and lower per capita usage, in particular in China, there are growing clinical demands and significant market potential for LMWH finished doses. Primarily driven by the increasing incidence of VTE and PE caused by the aging population, demands for LMWH finished doses will continually increase, which will result in a higher demand for heparin APIs.

INNOVATIVE DRUG MARKET

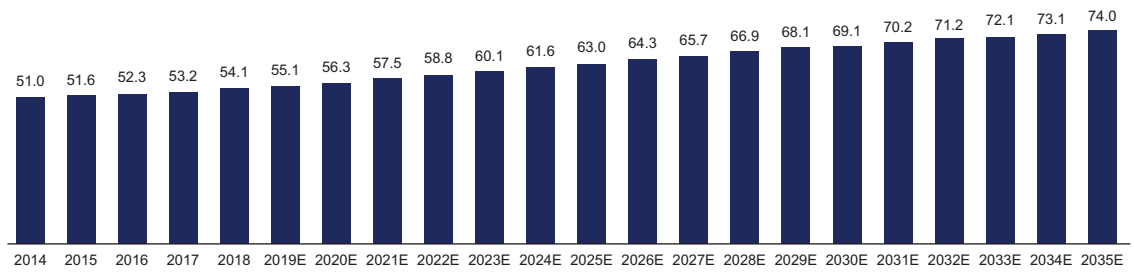
Oncology, anti-infectives, anti-inflammatory, diabetes and cardiovascular are among the therapeutic areas with the significant unmet medical needs worldwide due to its high mortality, high morbidity, or lack of effective treatments. Conventional therapies for these diseases are proven to be limited and many of the first-line treatments remained undeveloped for many years, and thus an increasing number of pharmaceutical companies, from multinational pharmaceutical giants to mid- to small-sized companies, have aggrandized their presence in the innovative drug market, and focused on the development of innovative treatment options, such as targeted therapies.

Ovarian Cancer

Ovarian cancer is a type of cancer that forms in or on ovaries, the female reproductive glands that produce eggs during a woman's reproductive years. Ovarian cancer may evolve from initial symptoms such as abdominal bloating, changes in appetite, pressure and pain in lower back and menstrual changes to ovarian cysts, masses or tumors. The following chart illustrates the historical trend and forecast of the incidence of ovarian cancer in China from 2014 to 2035:

The Incidence of Ovarian Cancer in China, 2014-2035E

	CAGR
2014-2018	1.5%
2018-2028E	2.2%
2028E-2035E	1.4%



Source: Frost & Sullivan Report

Ovarian cancer has large unmet medical needs due to poor prognosis and high mortality rate, lack of new first-line treatment and effective later line treatments. Ovarian cancer is the second most common gynecologic malignancy with a high mortality rate. The five-year survival rate of ovarian

cancer is 39.1% in China and 47.6% in the U.S. Conventional methods of treating ovarian cancer generally comprise a combination of chemotherapy and surgery. The first-line treatment for primary ovarian cancer is chemotherapy with carboplatin, docetaxel or paclitaxel, which has not been changed for more 10 years. Many women affected by advanced ovarian cancer respond to chemotherapy, but the effects typically are not long-lasting. The clinical course of ovarian cancer patients is marked by periods of remission and relapse of sequentially shortening duration until chemotherapy resistance develops. More than 80% of ovarian cancer patients experience recurrent disease, and more than 50% of these patients die from the disease in less than five years post-diagnosis. Bevacizumab in combination with chemotherapy has been approved for first-line therapy, resulting in a few months' delay in disease progression. The treatment however does not prolong the patients' life and may cause severe side effects.

PARP inhibitor (olaparib) is approved as first-line maintenance therapy for patients with deleterious BRCA mutations after showing response to first-line chemotherapy. Around 10-15% patients had BRCA mutations, leaving the rest of patients in need of new first-line treatment. Advances in checkpoint inhibitor therapy have gained speed in cancer care; however, ovarian cancer has yet to see any approved indications for immunotherapy agents.

Please refer to the section headed "Business—Our Innovative Drug Business—Oregovomab—Market Opportunity and Competition" for the details of competitive landscape.

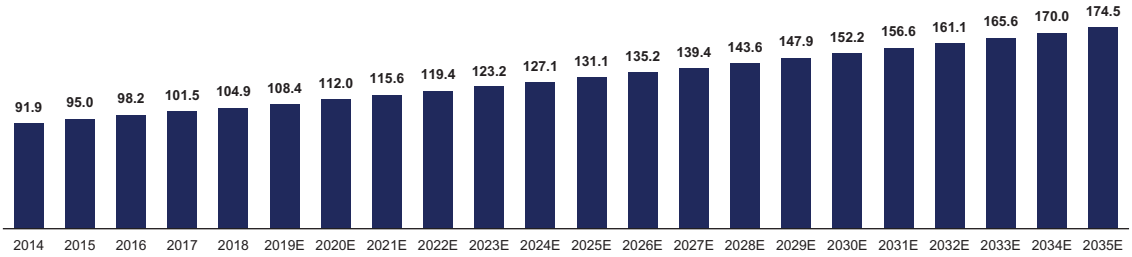
Pancreatic Cancer

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas, a large gland of the digestive system. Its symptoms include jaundice, sudden weight loss and digestive problems as early warning signs, and severe upper abdomen or back pain, extreme fatigue and diagnosed diabetes as advanced warning signs. The following chart illustrates the historical trend and forecast of the incidence of pancreatic cancer in China from 2014 to 2035:

The Incidence of Pancreatic Cancer in China, 2014-2035E

	CAGR
2014-2018	3.4%
2018-2028E	3.2%
2028E-2035E	2.8%

Thousand



Source: Frost & Sullivan Report

Pancreatic cancer has large unmet medical needs due to poor survival rate, and drug resistance developed after chemotherapy. Pancreatic cancer is one of the most lethal cancers worldwide. The five-year survival rate is only about 6% globally and 7.2% in China. It is difficult for the doctors to detect and prognose the development of pancreatic cancer at an early stage.

Main treatment methods for pancreatic cancer consist of surgery, radiotherapy, chemotherapy and interventional therapy. However, only around 10% to 15% of the patients are eligible for tumor resection, approximately 28% of the patients have chemotherapy as part of their primary cancer treatment. The options of targeted therapies are limited, most of which have not demonstrated expected efficacy.

In addition, most of the patients taking certain first-line drugs, such as gemcitabine, have been found to develop drug resistance. Recently, PARP inhibitor olaparib was approved in the U.S. as a first-line maintenance treatment of germline BRCA-mutated metastatic pancreatic cancer. However, only about 5%-8% of patients with BRCA mutation were benefited from such new treatment with a limited increase in progression-free survival.

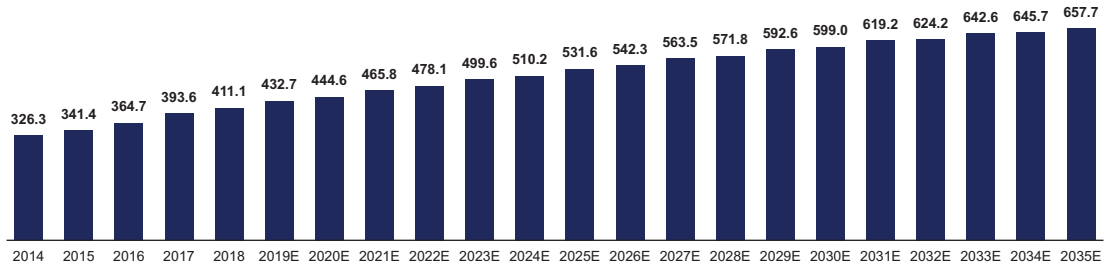
Please refer to the section headed "Business—Our Innovative Drug Business—mAb-AR20.5—Market Opportunity and Competition" for the details of competitive landscape.

VAP and HAP Caused by *Staphylococcus Aureus*

Ventilator-associated Pneumonia (VAP) is a type of lung infection that usually occurs 48 hours or more after the initiation of mechanical ventilation such as endotracheal intubation or tracheotomy. Hospital-acquired pneumonia (HAP) refers to any pneumonia occurring 48 hours or more after hospital admission. Both VAP and HAP can be caused by bacterium infection, such as infection from *Staphylococcus aureus (S. aureus).* The following chart illustrates the historical trend and forecast of the new cases of VAP and HAP caused by S. aureus in China from 2014 to 2035:

The New Cases of VAP&HAP in China Caused by *Staphylococcus aureus,* 2014-2035E

	CAGR
2014-2018	5.9%
2018-2028E	3.4%
2028E-2035E	2.0%



Source: Frost & Sullivan Report

Anti-infection therapy of VAP and HAP evolves from initial empiric antibiotic therapy, including antibiotics monotherapy and combined antibiotics therapy, to pathogen-specific antibiotic therapy. Methicillinresistant *Staphylococcus aureus* (MRSA) is one of the most common drug-tolerated pathogens for VAP and HAP, and glycopeptides and linezolid are two types of antibiotics that are commonly used for MRSA-specific therapies.

VAP is a high-mortality disease with the 30-day mortality rate reaching 28.4%. Intubation and ventilator support bypass the normal host defense mechanism, which increases the patients' risks of bacterial infection. Long term and repetitive use of the conventional therapeutic options, anti-microbial therapy may cause patients to develop drug resistance. HAP also has a high death rate with the 30-day

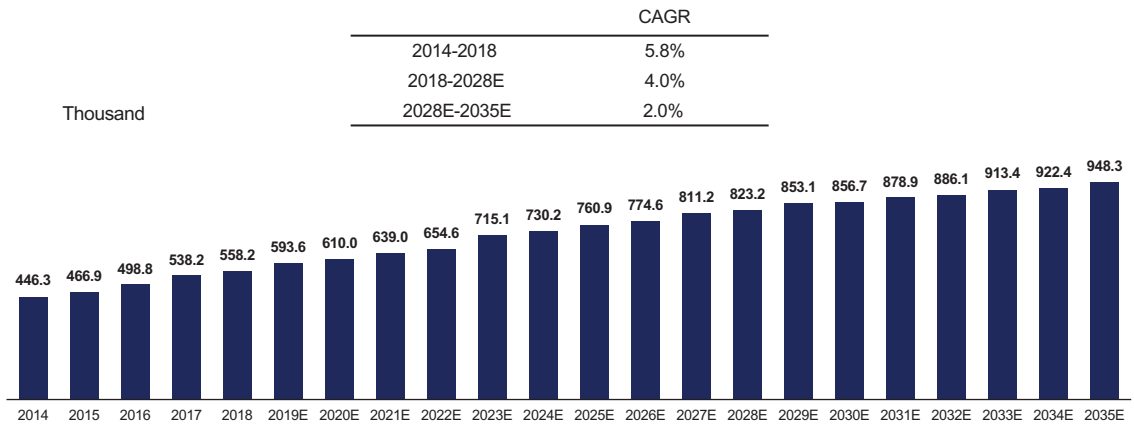
mortality rate reaching 23.9%. It is difficult to conduct clinical trials for patients with HAP because the enrolled patients have to undergo empiric antibacterial therapy at the same time, which may obscure the clinical results of the anti-bacterial drugs under study. In addition, anti-microbial resistance in major pathogens of HAP and VAP may ultimately result in treatment failure. Inappropriate anti-microbial therapy in both impatient and outpatient settings, has increasingly been recognized as a major cause of anti-microbial resistance that may contribute to VAP and HAP's high death rate. Anti-infective mAbs is a new class of anti-infective drugs that has the potential to become the standard of care, respectively, for active adjunctive treatment and prophylactic treatment of VAP and HAP due to its superior safety profile, a remarkably long plasma half-life period ranging from 11 to 30 days, and a low possibility of drug resistance.

Please refer to the section headed "Business—Our Innovative Drug Business—AR-301—Market Opportunity and Competition" for the details of competitive landscape.

VAP and HAP caused by *Pseudomonas aeruginosa*

Pseudomonas aeruginosa (P. aeruginosa) is a common pathogenic bacteria of VAP and HAP, which can be treated by specific antibiotics such as cephalosporin, carbapenem, ß-lactamase inhibitors, aminoglycosides and polymyxin. The following chart illustrates the historical trend and forecast of the new cases of HAP and VAP caused by P. aeruginosa in China from 2014 to 2035:

The New Cases of HAP&VAP in China Caused by *Pseudomonas aeruginosa*, 2014-2035E



Source: Frost & Sullivan Report

Anti-infective mAbs is a new class of anti-infective drugs that has the potential to become the standard of care, respectively, for active adjunctive treatment and prophylactic treatment of VAP and HAP due to its superior safety profile, a remarkably long plasma half-life period ranging from 11 to 30 days, and a low possibility of drug resistance.

Please refer to the section headed "Business—Our Innovative Drug Business—AR-101—Market Opportunity and Competition" for the details of competitive landscape.

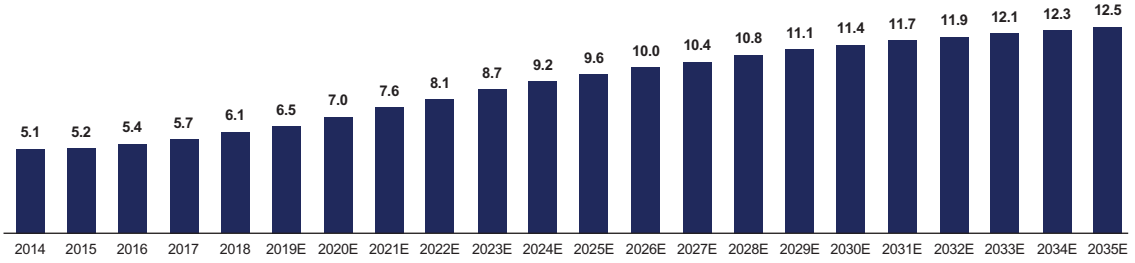
Type 2 Diabetes with CHD

Coronary heart disease (CHD) involves the reduction of blood flow to the heart muscle, resulting from build-up of plaque in the arteries of the heart. The most common symptoms of CHD are

angina and chest pain. The following chart illustrates the historical trend and forecast of diagnosed patients of type 2 diabetes with CHD in China from 2014 to 2035:

The Diagnosed Patients of Type 2 Diabetes with CHD in China, 2014-2035E

	CAGR
2014-2018	4.6%
2018-2028E	5.9%
2028E-2035E	2.1%



Source: Frost & Sullivan Report

Due to the high correlation between diabetes and cardiovascular diseases, an assessment and control of cardiovascular risk factors, such as hyperglycemia, hypertension and dyslipidemia, combined with an antiplatelet therapy, is necessary for the prevention and treatment of type 2 diabetes with CHD. Treatment options of cardiovascular disease includes many therapeutic agents, such as lipid lowering drugs, heart rate lowering agents and blood pressure lowering drugs. However, there still remains a large residual risk of major adverse cardiovascular events (MACE) for patients taking the current therapies.

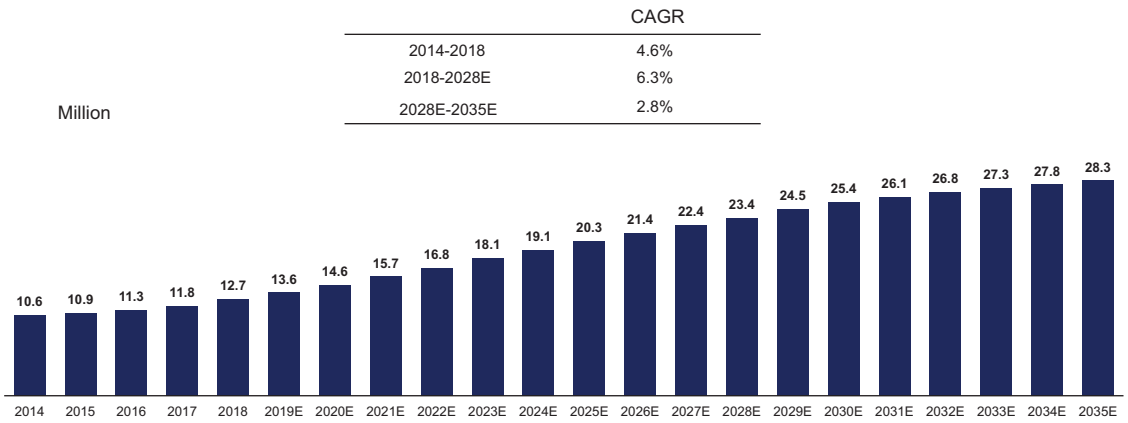
Despite of the high prevalence of type 2 diabetes with CHD in China, there was few cardiac prevention or rehabilitation program established in China. Even though the coronary death rates have decreased for decades, CHD death rates may increase in the near future because of the worldwide epidemic of obesity.

Please refer to the section headed "Business—Our Innovative Drug Business—RVX-208—Market Opportunity and Competition" for the details of competitive landscape.

Chronic Kidney Disease

Chronic kidney disease (CKD) refers to the gradual loss of kidney function. It is common, frequently unrecognized and may co-exist with other diseases, such as diabetes. CKD can progress to end-stage kidney diseases, and may even lead to death as severe complications are triggered. The following chart illustrates the historical trend and forecast of the prevalence of CKD in China from 2014 to 2035:

The Diagnosed Patients of Diabetic Kidney Disease in China, 2014-2035E



Source: Frost & Sullivan Report

In addition to nutrition and lifestyle therapy, which involves patient education, self-monitoring of blood sugar, diet adjustment and exercise, drug therapy is another treatment option for CKD, mainly focusing on glycemic control, anti-hypertension and lipid regulation.

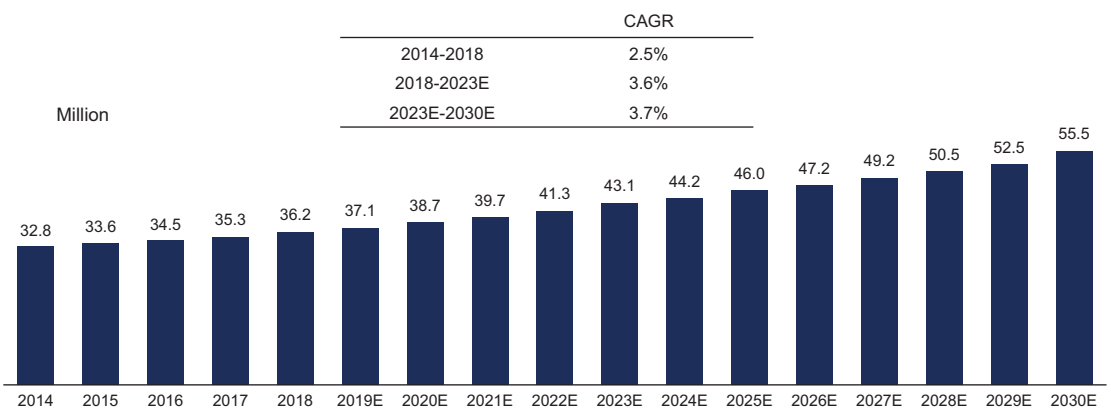
Diabetes is the leading cause of end-stage renal disease (ESRD) globally, accounting for approximately 40% of patients receiving renal replacement therapy each year. ESRD places a substantial economic burden on patients with treatment and rehabilitation expenses, and leads to loss in economic productivity and diminished social functions.

Please refer to the section headed "Business—Our Innovative Drug Business—RVX-208—Market Opportunity and Competition" for the details of competitive landscape.

Non-Alcoholic Steatohepatitis

Non-Alcoholic Steatohepatitis (NASH) is one of the most severe forms of non-alcoholic fatty liver disease. NASH may evolve from initial symptoms such as fatigue, weight loss and stomachache, to fibrosis, liver cirrhosis or even liver cancer. The following chart illustrates the historical trend and forecast of the prevalence of NASH in China from 2014 to 2030:

Prevalence of NASH in China, 2014-2030E



Source: Frost & Sullivan Report

NASH has huge unmet medical needs due to its large patient pool, no marketed drug, difficulties in developing drugs and cause for other severe diseases. With a prevalence of 24% worldwide, NASH is now the most common liver disorder. The increasing prevalence of NASH is related to the growing obesity epidemic and the disease is diagnosed in patients who have diabetes, high cholesterol or high triglycerides. Despite such a high prevalence rate, at present, there is no approved pharmacologic treatment for NASH. All the drugs applied are used to treat the complications of NASH, lower the risk of further progression, and prevent damages to the liver. Numerous obstacles make drug development for NASH treatment a challenge. The complexity of the pathogenesis of the disease, which involves multiple pathways, requires targeting of more than one pathway or a combination-based therapy. The complex interactions among numerous metabolic pathways, the immune system, and the gut prevent the development of a one drug-based therapy that can provide a cure for NASH. NASH is now considered to be the leading, and a rapidly increasing, cause of hepatocellular carcinoma, or primary liver cancer. More than 20% of patients with NASH progress to cirrhosis within a decade of diagnosis and, compared to the general population, have a ten-fold greater risk of liver-related mortality.

Changes in lifestyle, primarily through adjusting the diet and forming a habit of regular exercise, are currently the most effective method to treat NASH. Bariatric surgery can help relieve symptoms and lower the risk of developing cardiovascular diseases, but there was no evidence showing that bariatric surgery is able to treat NASH. Liver transplantation is also not a promising therapeutic option because of the limited liver sources and the high probability of recurrence in the transplanted liver.

Please refer to the section headed "Business—Our Innovative Drug Business—Pipeline Drugs of Our Portfolio Companies—HighTide's HTD1801—NASH" for the details of competitive landscape.

Heparanase Inhibitor

Heparanase is a heparin sulfate specific endo-ß-D glucuronidase. Studies show that enhanced expression of heparanase is observed in almost all types of cancer examined, which is tightly correlated with the tumor size, angiogenesis, metastasis and poor prognosis. Such finding placed heparanase as a type of cancer-associated enzyme. Clinical trials have been conducted for five sub-types of heparanase inhibitors globally, but only SST0001(roneparstat) and PG545 are still under clinical study.

SST0001 (roneparstat) is a modified heparin composed of 100% N-acetylated and 25% glycol split. Compared to unmodified heparin, roneparstat is able to inhibit the heparanase enzymatic activity with a decreased ability to release extracellular matrix-bound FGF-2. Roneparstat was well tolerated and safe at all the dose levels tested. Patients could be exposed to the drug at the dose levels of 200 and 400 mg/day without showing clinically relevant toxicities.

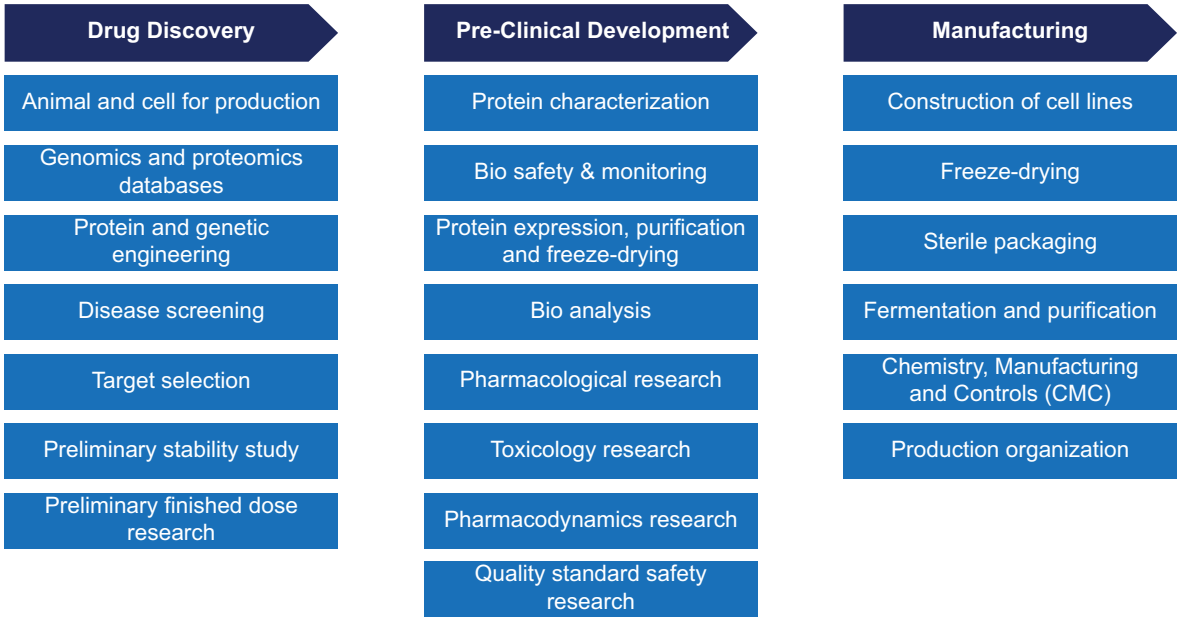
Heparanase inhibitors act on the heparan sulfate chain of the extracellular matrix (ECM), which plays an important role in tumor metastasis, tumor progression and the adjustment of tumor's micro-environment. Unlike conventional cytotoxic and targeted drugs, heparanase inhibitors are expected to have an integrated effect in inhibiting both tumor growth and tumor metastasis, and can be combined with cytotoxic drugs, targeted therapy or immunotherapy for cancer treatment.

Please refer to the section headed "Business—Our Innovative Drug Business—H1710—Market Opportunity and Competition" for the details of competitive landscape.

BIOPHARMACEUTICAL CDMO MARKET

Biologics CDMO Value Chain

Contract Development and Manufacturing Organizations (CDMOs) provide both customized pharmaceutical manufacturing services and high value-added services, such as drug development and optimization of the drug synthesis process. The two major types of CDMOs are pharmaceutical CDMOs and biologics CDMOs, the latter of which continually drives the growth of the overall CDMO market. Biologics CDMOs mainly focus on biological drug manufacturing, advancement of drug production technology and optimization of drug synthesis process. The following diagram illustrates the integrated value chain of biologics CDMO:



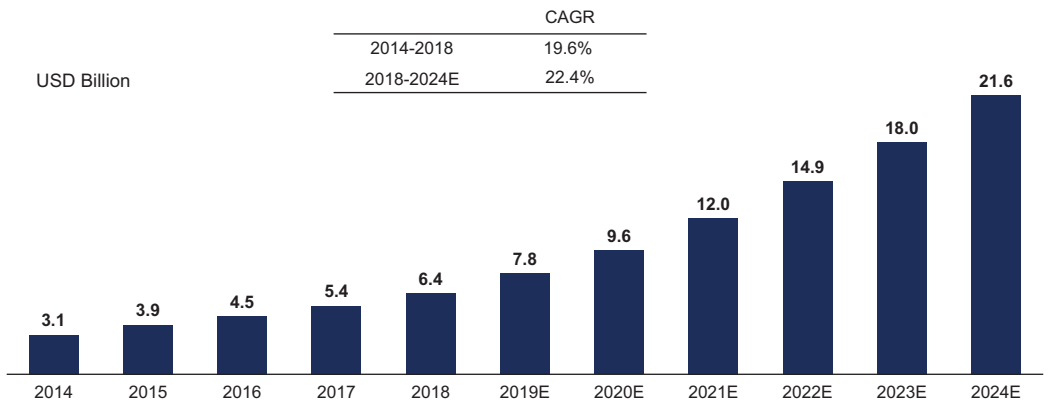
**Service offerings vary based on company's core strength and focus*

Source: Frost & Sullivan Report

Market Size

With the increasing investment in biologics industry and the emergence of small and mid-sized pharmaceutical companies focusing on the development of innovative biologic drugs, the global biologics CDMO market has expanded rapidly in recent years. Global revenue of biologics CDMO increased from US$3.1 billion in 2014 to US$6.4 billion in 2018, representing a CAGR of 19.6%, which is expected to reach US$21.6 billion in 2024 at a CAGR of 22.4%, as shown in the following chart:

Global Biologics CDMO Market Size and Forecast, 2014-2024E



Source: Frost & Sullivan Report

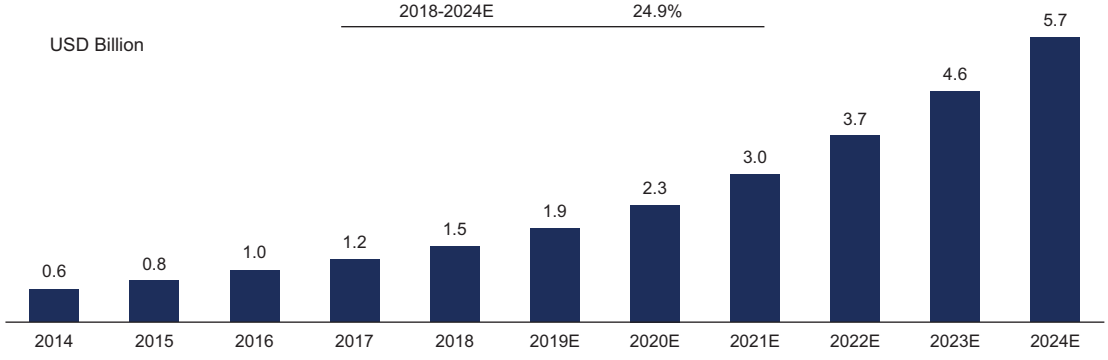
As the top five players of global biologics CDMO market in total accounted for a market share of 52.1% in terms of revenue in 2018, the global biologics CDMO market is generally believed to be not concentrated, suggesting significant market potential for small and mid-sized biologics CDMO companies. Additionally, as a growing number of pharmaceutical companies are developing biologics and more biosimilars are expected to enter the market, there will be huge demand for biologics CDMO service with significant growth potential.

Gene Therapy CDMO Market

The next generation of therapy, gene therapy, is a set of strategies that modifies the expression of an individual's genes or repair abnormal genes. Gene therapy has demonstrated substantial growth potential due to significant unmet clinical needs and recent commercial breakthroughs will further accelerate the growth of gene therapy. An increasing number of gene therapy focused CDMOs have been established to capture the growth opportunities of gene therapy market. The global gene therapy CDMO market increased from US$0.6 billion in 2014 to US$1.5 billion in 2018, at a CAGR of 23.4%, and is expected to reach US$5.7 billion in 2024, at a CAGR of 24.9%.

Gene Therapy CDMO Market, 2014-2024E[1]

	CAGR
2014-2018	23.4%
2018-2024E	24.9%



Source: Frost & Sullivan Report

[1] Gene Therapy includes cell and gene therapy

Plasmids DNA (pDNA) has been increasingly applied as non-viral vectors for gene therapy since 1990. The key mechanism of pDNA is endocytosis. Compared to viral and RNA-based vectors, plasmids are generally easier and cheaper to manufacture, transport and store and have a longer shelf life. The modular nature of plasmids also allows for direct molecular cloning, which enables it to become a superior vector for therapeutic use. The advantages of non-viral DNA vectors, such as pDNA, over viral vectors and RNA-based vectors have compelled researchers to improve their safety and utility for better clinical use. Because of the improved safety over viral vectors, pDNA has enabled a number of clinical trials.

The costs related to pDNA constitute the largest portion of variable costs for gene therapy production, which may exceed more than 60% when customized and CGMP-grade pDNA are used. Such high costs of production in addition to the increasing demand for pDNA due to its superior nature for gene therapy will encourage more CDMOs to enter the pDNA manufacturing field.

Competitive Landscape

The table below compares the major China-owned biologics CDMO operators in terms of their key capacities and market shares by revenue in 2018:

Company	Market Share in 2018	Key Capacities and Differentiations
Company A	55.8%	Company A offers end-to-end solution to discover, develop and manufacture biologics from concept to commercial manufacturing. Its service includes mAb discovery, bispecific antibody engineering, antibody drug conjugate discovery and cell line engineering and development.
Company B	23.6%	The business of Company B consists of four major arms, including life science CRO, enzyme and synthetic biology products, biologics development and manufacture, and cell therapy.
The Group	12.0%	The Group is a leading China-based pharmaceutical company with global businesses in pharmaceutical, innovative biotech and CDMO sectors. It operates CDMO business through two platforms. One CDMO platform enables the development and manufacture of recombinant pharmaceutical products and critical non-viral vectors and intermediates for gene therapy, and the other CDMO platform enables the development and manufacture of pharmaceutical products from natural sources.

Source: Frost & Sullivan Report

Entry Barriers

- *Ability to attract professional talents*—A full-service biologics CDMO business requires multi-disciplinary talents, such as R&D and sales professionals, to accomplish complex drug development, optimization of drug synthesis and other value-added services. R&D experts and strong sales force are crucial components of a successful CDMO, which help seek and secure collaboration opportunities. Hiring suitable R&D experts and in-house trainings to foster seasoned sales teams are time-consuming and involve high risks. New market entrants may find it difficult to compete for or cultivate such professional talents in the market.

- *Reputation for High Quality*—Biologics CDMO service providers are expected to not only complete the projects or provide the required services on time but also deliver high-quality products in compliance with the increasingly stringent regulations. New market entrants may find it challenging to establish a reputation for high quality in line with the evolving regulatory landscape.

- *High technical requirements*—Constant technical innovation is important for an established CDMO. For instance, the techniques of spray drying and continuous manufacturing can help a CDMO optimize the process and thus effectively lower the manufacturing costs. Such technical innovation requires a significant amount of R&D efforts and capital investment, which may hinder new players from entering into the market.

Growth Drivers

Global biologics market is expected to grow rapidly mainly driven by the superior efficacy of biologics, technological innovation, favorable government policies, increasing capital investment and emergence of small and mid-sized innovative companies as further discussed below. Such factors will therefore boost the demands for CDMO services for biologics and further drive the growth of biologics CDMO market.

- *Superior efficacy*—Biologics have demonstrated improved efficacy and fewer side effects in treating a broad spectrum of diseases that lacked effective therapies in the past, such as cancers and autoimmune diseases. The superior efficacy of biologics has led to an increasing acceptance of biologics among patients and doctors, which will generate strong market demand and stimulate the continuing growth of biologics market.
- *Advancement in Biotechnology*—Technological innovation in areas of genetics and biochemistry is crucial for the enhancement of a pharmaceutical company's in-house R&D capabilities. It also helps to increase the company's production yield and thereby lower the production costs. As such, advancement in biotechnology will continue driving the growth of the global biologics market.
- *Favorable policies in Emerging Markets*—The governments in developing countries have prioritized and designated the pharmaceutical industry as one of their "pillar industries" with the promulgation of favorable governmental policies and initiatives, such as expansion of the health insurance coverage and investment on medical infrastructure. As healthcare service and products become more accessible in those countries, the increasing sales in these markets will significantly contribute to the growth of global biologics sales in the next few years.
- *Increasing capital investment*—To maintain their leading market position, large pharmaceutical companies will continue to invest in both R&D and acquisition for innovative biologics candidates. Meanwhile, small and mid-sized pharmaceutical companies with a focus on innovative biologics are also able to attract more capital investment due to favorable governmental policies and increased public attention. Increases in global investment in biologics section will result in a rapid expand of biologics pipeline worldwide.
- *Emergence of Small and Mid-sized Innovative Companies*—With favorable governmental policies and increased capital investment, an increasing number of biotech startups have expanded their pipelines to innovative biologics. The competitive landscape of innovative biologics market will become less concentrated only among global pharmaceutical companies, as more market players are entering into the market. The increase in the number of market participants will stimulate the development of biologics market globally.

Future Trends

- *Developing Gene Therapy Focused CDMOs*—Approximately 7,000 rare diseases are identified worldwide, for which only 5% have FDA approved treatment options, indicating significant unmet medical needs. 80% of rare diseases are monogenic and gene therapy is becoming increasingly important for the treatment of rare diseases. In order to meet such growing demand, gene therapy focused CDMOs are indispensable to support the growing capacity and manufacturing technology demands.

- *Broader service coverage*—CDMOs will become a one-stop shop covering a broader range of services, from early-stage drug development to commercialization. Such broader service coverage will enable the CDMOs to meet the demand of pharmaceutical companies seeking to consolidate their processes and to diminish the transactions with multiple suppliers or outsourcing partners. Through strategic investment and innovative collaborations, continuous investment in CDMO R&D capabilities is able to attract customers at the early stage of their drug development process, and offer more value-added services at the later stage.

- *Industrialization of developing countries*—With the advantages of professional talents and lower manufacturing costs, CDMOs based in developing countries, such as China and India, have attracted the attention of many multi-national pharmaceutical companies ("**MNCs**"). As these CDMOs conform to the international standards, more orders from MNCs will be transferred to them.

- *Growing Importance of Biologics*—Therapeutic biologics have shown significant growth potential worldwide, primarily attributable to their superior efficacy and fewer side effects. Biosimilars will play an important role in the further expansion of the biologics market as the patent of some blockbuster biologic originators have expired. The in-house manufacturing capacity of the biopharmaceutical companies may not be sufficient to digest such growing demand and thus they have to outsource to CDMOs for drug manufacturing. In addition, as the drug structures are becoming more complex in the development of new drugs, pharmaceutical companies are increasingly relying on CDMOs for specialized expertise, which bolsters and secures the leading market position of CDMOs for the outsourced manufacture of biologics.

REPORT COMMISSIONED BY FROST AND SULLIVAN

In connection with the **[REDACTED]**, we have engaged Frost & Sullivan to conduct a detailed analysis and to prepare an industry report on the relevant industries in which we operate. Frost & Sullivan is an independent global market research and consulting company 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 included certain information from the Frost & Sullivan Report in this document because we believe such information facilitates an understanding of the heparin drug market for potential **[REDACTED]**. 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 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. Frost & Sullivan research may be affected by the accuracy of these assumptions and the choice of these primary and secondary sources.

Other bases and assumptions adopted by Frost & Sullivan in making its forecast include: (i) the social, economic and political environments of the EU, the PRC and the U.S. will remain stable during the forecast period, which will ensure a sustainable and steady development of the global healthcare

industry; (ii) the global healthcare market will grow as expected due to rising healthcare demand and supply; and (iii) the global government will continue to support healthcare reform.

We have agreed to pay Frost & Sullivan a fee of RMB500,000 for the preparation of the Frost & Sullivan Report. The payment of such amount was not contingent upon our successful **[REDACTED]** or on the content 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 confirm that after taking reasonable care, there has been no adverse change in the market information since the date of the report prepared by Frost & Sullivan which may qualify, contradict or have an impact on the information set forth in this section in any material respect.