Study on the Market Environment of Heparin and Development Suggestions in China Based on the PEST Model

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Abstract

Objective To analyze the market environment of heparin, and to provide reference for the development of the heparin industry in China. **Methods** The international market size and competition pattern of heparin was investigated first. Then, environmental analysis of it was made based on the PEST model. **Results and Conclusion** There is room for optimization of the relevant policies for the development of heparin industry in China. The use of heparin drugs and regulation should be further improved. In addition, the research and development ability of pharmaceutical enterprises should be enhanced, and the development strategy of heparin industry needs to be adjusted.

Keywords: heparin; market competition; PEST analysis

Heparin usually refers to heparin sulfate, and its chemical composition is a highly sulfated linear heteropolysaccharide (acid mucopolysaccharide) composed of disaccharide repeating units linked by hexuronic acid (HexA) and glucosamine (GlcN) through α-1,4 glycosidic bonds [1].

1 Studies related to heparin

Heparin is an anticoagulant and antithrombotic drug widely used in clinical practice today, and it is also the most commonly used natural therapeutic drug after insulin.

In 1916, McLean purified an anticoagulant from the organs and tissues of mammals, which could be used as a drug. When it was discovered, it was named "enkephalin". Subsequently, Howell, McLean's mentor, improved the above purification method in 1918, and finally named the anticoagulant "heparin". The first crude products of heparin were extracted by acetone precipitation in 1925. Heparin was identified as a sulfur-containing sugar in 1928. The purification process was significantly improved in the 1930s by Charles and Scott, who also changed the tissue source from dog or bovine liver to bovine lung, which was cheaper and higher in yield. After passing clinical trials in 1935, it was used as a first-line anticoagulant and antithrombotic drug.

Heparin was identified in 1939 as a poly sulfate of a polysaccharide composed of glucosamine and uronic acid. In 1961, Nomine, et al. demonstrated that the disaccharide repeating unit of heparin was composed of iduronic acid (IdoA) and GlcN linked by α-1,4 glycosidic bond, thus forming a linear backbone structure. In 1968, Perlin proved by nuclear magnetic resonance (NMR) that IdoA was the main class of uronic acid in heparin, and clarified that glucuronic

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acid (GIcA), the isomer of IdoA, also existed in the main chain of heparin.

Interest in the application of low-molecular-weight heparin began in the 1970s, when it was found that the activity of small molecular sugar chains separated by gel was higher. At the same time, the production of heparin in China began in the late 1970s when China's pharmaceutical industry started to take off. Subsequently, a variety of methods for cleaving heparin emerged. In 1982, the first clinical study of low-molecular-weight heparin (LMWH) was carried out. It was found that low-molecular-weight heparin had smaller weight, more controllable anticoagulant properties, and could act subcutaneously, with less side effects and long half-life. From then on, it has gradually replaced unfractionated heparin as the most important clinical anticoagulant product.

Currently, more than half of the heparin on the market is used to prepare LMWH, and these heparin-based drugs are essential in the treatment of thrombosis, embolism, and prevention of coagulation during surgery. China has begun the development of low-molecular-weight heparin products since the 1990s. Heparin has been used in clinical practice for more than 80 years, which makes people pay more attention to the stability and safety of the heparin supply. In recent years, with the aging of the global population, the rapid increase in the number of diagnosed venous thromboembolism (VTE) cases, and the increasing demand for prevention and treatment in COVID-19, the demand for antithrombotic drugs has been on the rise.

2 Clinical application of heparin

Heparin is the most effective and largest dosage anticoagulant drug in the world. Heparin preparation can be used in various departments before interventional therapy.

Unfractionated heparin (UFH) is mainly used for anticoagulant treatment in hemodialysis, catheterization, extracorporeal circulation, microvascular surgery, and other operations, as well as the treatment of disseminated intravascular coagulation and thrombosis. However, it also has side effects such as bleeding complications, thrombocytopenia, and osteoporosis. Now it is often replaced by low-molecular-weight heparin in clinical practice. Standard heparin is mainly used as an indwelling needle sealing fluid to maintain venous catheter patency and reduce extubation rate.

LMWH is mainly used to treat acute venous thrombosis and acute coronary syndrome (angina pectoris, myocardial infarction, etc.). At the same time, the role of LMWH in the anticoagulant therapy of obstetrics and gynecology, reproductive medicine, and other departments has become increasingly prominent. LMWH has significant advantages over UFH and it gradually replaces standard heparin formulations. Heparin has a strong anticoagulant and antithrombotic function, such as anti-IIA and anti-Xa function. Besides, it also has a variety of biological functions such as lowering blood lipids, anti-atherosclerosis, anti-proliferation of media smooth muscle cells (SMC), anti-inflammation, anti-allergy, anti-virus, and anti-cancer, so it is commonly used. Low-molecular-weight heparin preparation has a wide range of biological functions due to its small molecular weight and difficulty in being neutralized by factor IV, stronger anticoagulant effect, and fibrinolysis [2], as shown in Table 1.

3 Analysis of global heparin market

3.1 Market size and pattern of global heparin active pharmaceutical ingredient (API)

3.1.1 Market size

According to statistics, the global market sales of heparin API was about US $3.332 billion in 2023, and the global sales of heparin API are expected to reach US $3.825 billion in 2024, with a growth rate of 21.7% from 2018 to 2024. Rising heparin API prices will drive the growth of the global market of heparin API. According to relevant forecasts, the growth trend will increase until 2027, with global sales reaching US $6.246 billion [3].

Table 1 Clinical application of heparin preparations

Department	Clinical application
Cardiology	Acute coronary syndrome (unstable angina, acute myocardial ischemia), thrombolysis in acute myocardial infarction, post-stenting, other organic heart disease (dilated cardiomyopathy, mitral stenosis, atrial fibrillation, endocarditis)
Department of Respiratory	Chronic obstructive pulmonary disease, acute and chronic pulmonary heart disease, pulmonary embolism, acute and chronic asthma, emphysema complications
Department of Neurology	Treatment of iron deficiency cerebral infarction, transient ischemic attack
Renal Medicine	Glomerular disease, proliferative nephritis, dialysis anticoagulation
The Orthopedic	Hip and knee replacement surgery, fracture surgery, prevention of venous thromboembolism
General Surgery	Surgical prevention of venous thromboembolism and pulmonary embolism
Department of Oncology	Surgery to prevent venous thromboembolism, and pulmonary embolism, reduce transfer to the distal vascular tumor cells
Gynecology	Pregnancy complicated with thrombotic disease, amniotic fluid embolism, and intrauterine stillbirth
Pediatric	Cardiac catheterization for congenital heart disease, refractory nephrotic syndrome, bronchial and pulmonary disease
Others	Geriatrics; Burns; Hematology; Hepatology; Emergency Department

3.1.2 Market pattern

The competitive pattern of the global heparin API industry is highly concentrated. Due to the large-scale intensive pig breeding and slaughter in the United States and European Union, nearly all small intestines of pigs have been used for the production of crude heparin , so there is little room for improvement in the production of crude heparin in the United States and European Union. China's heparin API production ranks first in the world. According to Frost & Sullivan, the global heparin API supply market is highly concentrated and mainly located in China [4]. The major manufacturers of heparin APIs in European Union include Sanofi, Leo, Biofer, and Opocrin (See Table 2).

Table 2 Global heparin API suppliers

Countries and regions	Company name	Related businesses
The United States	Pfizer	The main supply of APIs is its preparation production, a small number of external sales
	SPL	The main supply of raw materials is its preparation production
Europe	Sanofi	The main supply of APIs is its preparation production
	Leo	
	Bioiberica	Bulk pharmaceutical products are mainly exported, the largest supplier of bulk pharmaceutical products in Europe
China (Major supply areas)	Hepalink	APIs are mainly exported to originators such as Sanofi and customers in the United States
	Health Friends Inc.	60% of APIs are exported to the originator and the United States; 40% are exported to Europe and other markets
	Changshan Pharmaceutical	APIs are mainly exported to other markets such as Europe
	Dongcheng Pharmaceutical	
	Qianhong Pharmaceutical	

3.2 Market size and pattern of global heparin preparations

3.2.1 Market size

Heparin formulations include standard heparin formulations, low molecular weight heparin formulations, and fondaparin formulations, among which low molecular weight heparin formulations account for more than 90% of the market share. In 2023, the global heparin preparation market size was about US $6.198 billion, of which the market size of low molecular heparin preparation was about US $5.535 billion, accounting for nearly 90% [5].

3.2.2 Market pattern

Low molecular weight heparin preparations still occupy the main sales share in the heparin preparation market, accounting for 85.91% of the total sales of heparin preparations in 2019. Standard heparin preparations maintain an irreplaceable role in traditional anticoagulation such as cardiac surgery, accounting for 14.09% of the total sales of heparin preparations in 2019.

For a long time, with the help of traditional brand products, Sanofi, Pfizer, GlaxoSmithKline, and other enterprises have dominated the market of enoxaparin sodium, dalteparin sodium, and nadroparin calcium, which are the three mainstream low molecular weight heparin formulations. From the overseas classification of low molecular weight heparin, five categories of low molecular weight heparin, namely enoxaparin sodium, nadroparin calcium, dalteparin sodium, parparin sodium, and tiparin sodium were included in the United Kingdom and European pharmacopeia as shown in Table 3.

Table 3 Major global suppliers of heparin preparations

Preparation	Name of company	Related businesses
Low molecular weight heparin dominates the heparin preparation market	Sanofi	It mainly sells injectable enoxaparin
	Pfizer	It mainly sells dalteparin sodium injection
	GSK	The main sales of nadroparin calcium injection
	Sandoz	To achieve imitation of enoxaparin
	Amphastar	
	TEVA	
Standard heparin	APP	Standard heparin market dominance in the United States
	Hospira	
	Sagent	The leading manufacturer of global standard heparin
	Pfizer	The leading manufacturer of global standard heparin
	Rationpharm	The leading manufacturer of global standard heparin
	B. Braun	The leading manufacturer of global standard heparin

4 Import and export of heparin products in China

From the perspective of import data, it can be seen that the demand for heparin products has increased due to the impact of the pandemic, and the import volume of heparin products (mainly crude heparin products) increased significantly in 2021 and 2022, and the average price continued to rise [5]. See Table 4 for data content.

Table 4 Quantity price trend of crude heparin imports in China from 2020 to 2023

Year	Import volume (kg)	Import amount ($)	Average price (USD/kg)
2020	11 551	62 866 141	5 442.51
2021	29 416	201 692 870	6 856.57
2022	37 935	223 527 393	5 892.38
2023	15 412	83 120 203	5 393.21

In recent years, the import regions of heparin products from China mainly include the European Union, South America, North America, East Asia, Southeast Asia, etc., of which the European Union occupies the largest share. From the analysis of export volume, the export products are mainly heparin sodium, which are used in pharmaceutical preparations and other fields. The export of heparin and its sodium is mainly concentrated in Asia, Europe, and North America, accounting for 89% of China's total export of western pharmaceutical raw materials. Asia and Oceania, which includes 10 member countries of ASEAN, the main signatory of RCEP, and 15 member countries such as Japan, China, New Zealand, Australia, and South Korea, accounted for the main share of exports.

5 PEST analysis of heparin market and industry development in China

5.1 Analysis of political environment

5.1.1 Government policies

Due to the large number of patients with cardiovascular disease, China attaches great importance to the development of heparin drugs. From the perspective of the overall planning of biomedicine, the "Guidelines for the Development of Pharmaceutical Industry" and other related policies have accelerated the scientific and technological progress in biomedicines and promoted the production of heparin drugs in China. In terms of the structural adjustment of the biomedical industry, the "Healthy China 2030 Initiative" "Opinions on Reforming and Improving the Supply Security and Use Policy of Generic Drugs" and other policies put forward the reform of biochemical and medical health system to promote the entry of generic drugs such as heparin into clinical use as soon as possible. From the perspective of drug evaluation and approval, the "Opinions on Reforming the Evaluation and Approval System for Drugs and Medical Devices" "Opinions on Deepening the Reform of the Evaluation and Approval System to Encourage the Innovation of Drugs and Medical Devices", and other policies put forward the standardized management of drug production license, drug registration application, drug standards, and drug prices. These policies can greatly promote the development of the biomedical industry, including the heparin drug industry.

5.1.2 National centralized procurement bidding

In 2023, the first national centralized procurement of drugs – the eighth batch of national centralized procurement came to an end. Anticoagulant heparin products entered the national centralized procurement catalog for the first time, and nadroparin injection and enoxaparin injection were officially included. Among them, the results of the proposed selection showed that a total of 4 enterprises won the bid for nadroparin injection, 9 enterprises won the bid for enoxaparin injection, and Sanofi and Aspen, the original manufacturers of enoxaparin and nadroparin, participating in the bidding, were all excluded [6]. The failure of the centralized drug procurement of the original manufacturer made room for the substitution of domestic heparin formulations. Sanofi and Aspen once occupied more than one-third of the market share

of enoxaparin and nadroparin.

5.2 Analysis of economic environment

For domestic heparin enterprises, heparin market competition is fierce, it is easy to lead to the decline of profit margins under the premise of ensuring the quality and reducing cost to maintain competitiveness, affecting the sustainable development of enterprises. Since 2023, China's macroeconomic recovery has improved, and high-quality development has made solid progress. China is in the transition period of economic operation mode, and it has shifted from the high-speed growth stage of the low-cost period to the high-quality development stage of the high cost. The mode of economic development is shifting from extensive growth of scale and speed to intensive growth of quality and efficiency. The economic structure is changing from a focus on incremental growth and capacity expansion to a deep adjustment of growth. The driving force of economic development is shifting from traditional growth points to new growth points.

Among the antithrombotic and anticoagulant drugs in hospitals, heparin and low molecular weight heparin are still commonly used in China. Anticoagulant drugs can reduce the concentration of coagulation factors, thereby reducing blood coagulation or hypercoagulation state, preventing thrombosis, or preventing the development of thrombosis. As the economy recovers, people pay more attention to their health. With the expansion of drug clinical use, heparin shows a rising trend year by year, which also drives the market of heparin raw materials and its preparations to rise [7].

5.3 Analysis of social environment

Heparin drugs, as important anti-thrombotic and anti-coagulation drugs for the treatment of cardiovascular diseases, benefit from the growth of market demand in European Union, the United States, and other markets. Therefore, the global market demand for heparin drugs is on the rise. In recent years, with the increasing number of aging population, the number of patients with cardiovascular disease in China has been increasing, which directly drives the overall market demand for the heparin industry [8].

The increased awareness of anticoagulation and more medication demand will definitely expand the heparin drug market. In developed countries in European Union and North America, people's awareness of preventive anticoagulation has been popularized, and various departments of hospitals generally use anticoagulant drugs for targeted prevention and treatment before, during, and after surgery. However, in China, the function of heparin drugs as general medication has not been fully developed. Besides, patients and doctors have insufficient understanding of heparin, which may lead to improper use or unreasonable prescription [9].

5.4 Analysis of technical environment

China has the production capacity of the whole industry chain from crude heparin to heparin raw materials, and then to heparin preparations. In addition, the production scale of multiple products in each link is large, which has the advantages of the whole industry. In the past decade, with the huge demand for heparin in the international market, China's heparin drug manufacturers continuously increased their investment in production technology optimization and product research and development, which also made major technological breakthroughs in heparin preparations. The complete industrial chain of the heparin drug industry in China has gradually formed. They even expand business to international markets.

Enzymatic hydrolysis and ion exchange are the main technologies used in heparin extraction in China. However, there are still great differences in the technology and process among different enterprises. The specific operation and technical parameter control ability in protein removal method, ion exchange technology, molecular weight control, and other

aspects are not the same, resulting in different yields. In addition, due to the different methods adopted in impurity removal, the impurity content and quality stability of products are also various [10].

Although China is the biggest country in the production and export of heparin raw materials, the production of crude heparin products and heparin preparation are only in the upstream of the whole industry chain, which has the least profit space and low added value. Therefore, China is not dominant in the heparin industry in the downstream. At the same time, the technical level of the crude heparin is relatively low, and the quality of heparin product is uneven. Most of the crude heparin enterprises are developed from extensive processing workshops, and the product preparation process is accompanied by a large amount of organic wastewater, which has adverse effects on the environment.

6 Development strategy of the heparin industry in China based on the PEST analysis model

6.1 Optimizing the relevant policies and systems of heparin industry

Under the background of national procurement policy, enterprises are encouraged to increase investment in research and development ability and their technical level. Meanwhile, the market-oriented mechanism of technological innovation should be improved to accelerate the development and listing of product innovation. Therefore, enterprises can form a technological innovation system by taking market as the guidance, and fastening deep integration of production, education, research and application. In the face of the development and transformation of heparin industry, strict rules and regulations should be established to promote the green production of heparin. Local governments should support the transformation and innovation of the heparin industry according to the actual situation. Besides, the government should coordinate leading enterprises, universities, and research institutes to establish several key technology platforms. Pharmaceutical enterprises can actively participate in international cooperation and competition to carry out comprehensive research and development of heparin with greater therapeutic potential and minimal side effects.

Domestic pharmaceutical enterprises should increase investment in research and development, improve their R&D level of innovative drugs, and accelerate the scale-up process of heparin generic drugs based on the promotion of policies such as “procurement with quantity” and “consistency evaluation”. At the same time, pharmaceutical enterprises should respond to the encouragement and support of the policy environment for innovative drugs, continuously enrich their product types, and innovate industrial technology.

6.2 Making great efforts to improve the efficiency of supervision

In terms of production and circulation, product quality and safety are the lifeline of the heparin industry. Since domestic crude heparin has experienced a process from small workshop production to large-scale centralized production, the effective supervision of the crude heparin process chain is of great significance for the safety, effectiveness, and quality control of heparin raw materials and preparations. As to the use of heparin products, the dosage of heparin needs to be precisely controlled to avoid adverse reactions caused by excessive or insufficient use. Regular qualification verification and training should be carried out for medical staff to ensure the correct use of heparin products.

China’s heparin industry is highly concentrated and the entry barriers of new enterprises are high. In addition, the strict quality control gradually eliminates enterprises with low technical levels and poor product quality. These enterprises should adhere to seeking progress in stability, comprehensively expanding domestic demand and deepening the supply-side structural reform, promoting domestic and international double circulation, and continuously

improving the quality and quantity of heparin drugs in China.

6.3 Promoting the hierarchical medical system and expanding the scale of demand

In China, low molecular weight heparin is mainly used for anti-thrombosis, while the amount of venous thrombosis prevention in postoperative patients is less. Since decentralization of medical services in China mainly focuses on improving the hierarchical medical system, primary medical institutions are mainly responsible for diagnosis and routine disease management, while larger and higher-level hospitals focus on the treatment of complex or critical diseases, thus limiting the effectiveness of the medical and health system. Therefore, the hierarchical medical system should be further improved to maintain the continuous growth of the antithrombotic drug market in China. Thus, the use of heparin therapy will be widely accepted for the prevention of postoperative venous thrombosis and acute coronary syndrome, as well as anti-tumor adjuvant therapy. Under the background of the improvement of national health awareness and the change of doctors' clinical medication concept, heparin drugs will be more used to prevent coagulation and thrombosis, and the purpose of general medication will be realized. In the future, the demand scale for low-molecular-weight heparin preparations in China will continue to expand.

6.4 Accelerating the informatization construction of heparin enterprises

On the surface, the lack of endogenous demand in the heparin drug market is cyclical. One of the most typical features in 2023 is the extended heparin drug inventory cycle, with a long period of destocking, significantly longer than any period in history. The lack of total demand is an important manifestation of the imbalance between supply and demand. Therefore, pharmaceutical enterprises need to strengthen information construction, paying attention to the linkage of stock and increment, and taking the stock and increment market as a whole.

6.5 Learning from successful experiences and exploring a suitable development path for pharmaceutical enterprises

Domestic heparin enterprises should strive to realize the integration of heparin raw materials and preparations and improve the added value of the industrial chain. Drawing on the successful experience of enterprises such as Hepalink and Healthy Friend Inc., pharmaceutical enterprises can carry out strategic layouts according to their specific conditions, increase the efforts of clinical trials, and strive for more heparin products to be listed and registered. At the same time, these enterprises should try to expand the international market. By understanding the international market demand and regulatory requirements, they can promote the export of heparin drugs and enlarge their market share.

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