



Plasma fractionation in China: progress and challenges

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Abstract: China is one of the largest consumers and manufacturers in the global plasma-derived products market and serves a huge population of more than 1.3 billion. Both blood and plasma-derived products are regarded as strategic resources in China. Great progress has been made in the Chinese plasma fractionation industry in the past 50 years, while problems still remain. Self-sufficiency and strategic independence of plasma-derived products has not yet been achieved. Reviews of Chinese plasma fractionation have seldom been published. The Chinese experiences with plasma fractionation may, however, lend lessons to other developing countries, especially countries along the Belt and Road routes, as well as contribute to global improvements on plasma fractionation.

Keywords: China; blood; plasma fraction

Received: 31 October 2017; Accepted: 10 January 2018; Published: 26 February 2018.

doi: 10.21037/aob.2018.02.02

View this article at: <http://dx.doi.org/10.21037/aob.2018.02.02>

Currently, China is one of the largest consumers and manufacturers in the global plasma-derived products market. This regional market is growing at a rapid pace with the increasing demands of a huge population of more than 1.3 billion.

There are two independent blood service systems in China: the voluntary non-remunerated whole blood banking system and the commercial source plasma collection system. Whole blood and apheresis platelets collected from the voluntary non-remunerated whole blood banking system are used directly in clinical transfusion, while commercial source plasma is fractionated into plasma-derived products. There is no non-paid plasma donor in China. Plasmapheresis centers were state-owned, just like voluntary non-remunerated blood centers, before 2006. Nevertheless, the “Working Plan on Transformation of Plasmapheresis Centers” was issued by nine national ministries and commissions in 2006 (1), as management methods changed when ownership was transferred from local governments to plasma fractionation enterprises.

Legislative framework and management system

The Chinese blood donation law established in 1998 is

the only law pertaining to blood donation and clinical transfusion and was a true milestone for the Chinese blood services system, followed by the issuance of a series of regulations and standards that have become the guiding principles to ensure plasma adequacy and safety (*Figure 1*). They set requirements on plasma donation sessions and donor selection criteria, and they established quality standards for plasma collection, storage and transportation.

The National Health and Family Planning Commission of the PRC (previously the MOH) is the competent authority for plasma collection management. The China Food and Drug Administration (CFDA) is responsible for fractionation and sales. The national regulatory framework is continuously changing in order to keep up with the evolving domestic needs. Plasma fractionation enterprises have taken charge of the quality of both plasma and its products.

The set up of commercial collection entities by plasma manufacturers should be in accordance with local government plans, strictly meet the relevant standards and requirements, and pass inspection for approval. All of the collection entities were established in counties with donors restricted to local residents.

National and regional supervisory visits or inspections

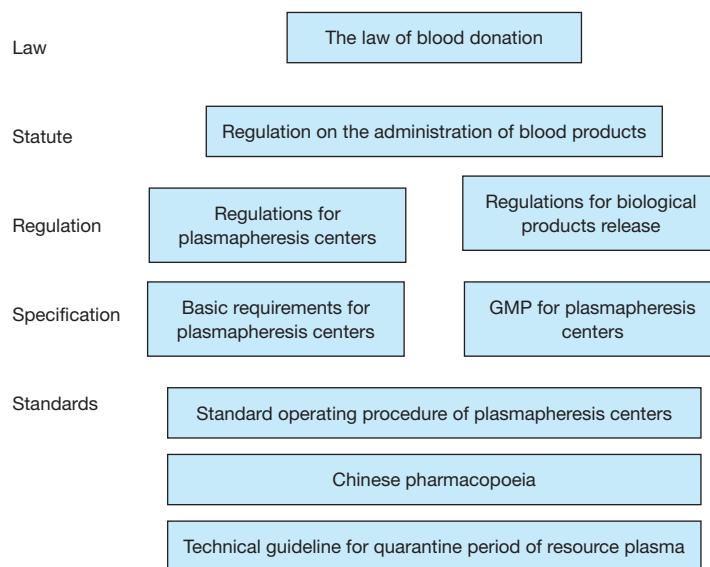


Figure 1 Legislative framework of plasma fractionation.

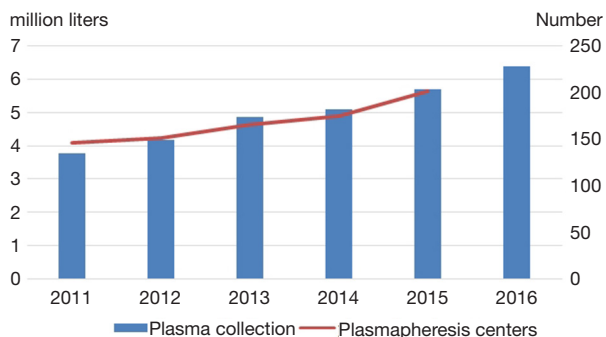


Figure 2 Volume of plasma collection and number of plasmapheresis centers from 2011 to 2016.

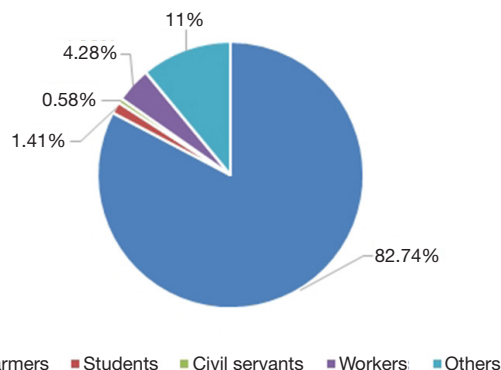


Figure 3 Proportion of registered donors by occupation.

were organized periodically as a sustainable mechanism to monitor blood services management. The subjects of inspection included policy implementation, quality management, improvement of services, and focusing on processes to outcomes. Covering “vein-to-vein”, these supervisory visits greatly facilitated improvements to blood safety and provided an effective method of surveillance and continuous advocacy for blood safety (2).

Plasma collection

There were 201 commercial plasmapheresis centers by the end of 2015, which contributed about 6 million liters of source plasma for the manufacture of plasma-derived

products (3). Plasma collection showed a steady trend of linear growth from 2011 to 2016 (3-6). It is more significant that registered donors maintained rapid growth over the past five years, although there has been a small increase in the number of plasmapheresis centers (Figure 2).

The distribution of donors across China as a whole (all donors were paid) consisted mainly of farmers, accounting for 82.74% of the total, with the proportion of workers, civil servants and students being extremely low (Figure 3).

Stations could only collect the plasma of certain people in their defined areas, and the government set up a strict standard for donor selection. In order to maintain donor safety, a most rigorous plasma collection frequency has been implemented, which is, namely, at least 14 days before the

Table 1 Technological trends in the manufacturing processes of IVIg and factor VIII

Products	Technological trends		Virus inactivation/removal	
	Before 2000	After 2000	Before 1998	After 1998
IVIg	Ethanol precipitation	Ethanol precipitation + ion exchange chromatography	None	Low pH (pH 4.0) treatment + pasteurization or nanofiltration
Factor VIII	Cryoprecipitate + acid precipitate + Al(OH) ₃ absorption	Cryoprecipitate + acid precipitate + Al(OH) ₃ absorption + ion exchange chromatography	None	Solvent-detergent + vapor heat or dry heat

IVIg, intravenous immunoglobulin.

next donation (7).

Plasma donors in China are tested for their hemoglobin concentration, ABO group, HBsAg, hepatitis C virus (HCV) antibodies, alanine aminotransferase (ALT), HIV-1 and HIV-2 antibodies, and antibodies to treponemal antigens. Donors with reactive results to transfusion-transmitted viruses are permanently deferred. All of the plasma tests should have adopted nucleic acid testing (NAT) by the end of 2019 (8), which will further improve the safety of source plasma.

To ensure the safety of plasma, a quarantine period has been implemented since 2008 (9), which means that plasma must be stored for 90 days after collection, after which the donor's blood is tested again. If the tests are negative, then the plasma collected 90 days prior may be released for production. This helps to avoid the threat of the "window period" and achieve a maximum level of plasma safety.

Technologies

In China, plasma derivatives were first produced in the 1960s by the Institute of Blood Transfusion and the Shanghai Institute of Biological Products using the Kistler/Nitschmann (10) and Cohn (11) plasma fractionation methods, respectively. Subsequently, "the cold ethanol precipitation method of plasma fractionation and its clinical application" passed the technical appraisal organized by the Chinese Ministry of Health in 1966 (12). Due to the economic situation and the need for combat readiness, the method of rivanol fractionation as a convenient, simple, and inexpensive procedure was widely adopted by most fractionators from the early 1970s, a procedure later annulled in 1995. Although plasma derivatives have been fractionated for about 50 years, large-scale production started relatively late (from the 1990s) and lagged in China compared with the developed countries. From the 1990s to

the 2000s, most plasma fractionation plants used the cold ethanol fractionation precipitation procedure developed by Cohn (11) and modified by Kistler and Nitschman (10). In the meantime, a 90-day quarantine period (13), virus inactivation/removal technology (14) (including solvent/detergent treatment, dry heat, pasteurization, low pH incubation, nanofiltration, and so on; see *Table 1*), and the lot release of plasma-derivatives (13) were implemented to increase the safety against blood-borne viruses. Although the methods for plasma fractionation are getting more and more complicated (such as introducing the use of chromatography, depth filtration and ultrafiltration) after more than 50 years of development in China, the current core fractionation technology still critically relies on the cold ethanol precipitation process. It is worth noting that with the exception of just a small number of manufacturers producing intravenous immunoglobulin (IVIg) and coagulation factors by a process of integrated chromatography to cold ethanol precipitation (*Table 1*), most Chinese fractionators still use the method of cold ethanol precipitation to obtain albumin and IVIg. Progressively, a few manufacturers have introduced chromatographic technology to research and develop new protein therapeutics, such as obtaining antithrombin III from Cohn fraction IV by combining ion exchange chromatography with heparin affinity chromatography, isolating protein C from cryo-poor plasma using the combination of ion exchange chromatography with heparin affinity chromatography, and separating the von Willebrand factor from cryoprecipitate undergoing two ion exchange chromatographic processes.

Plasma fractionation

As a result of not having any requirements on good manufacturing practice for pharmaceuticals (GMP),

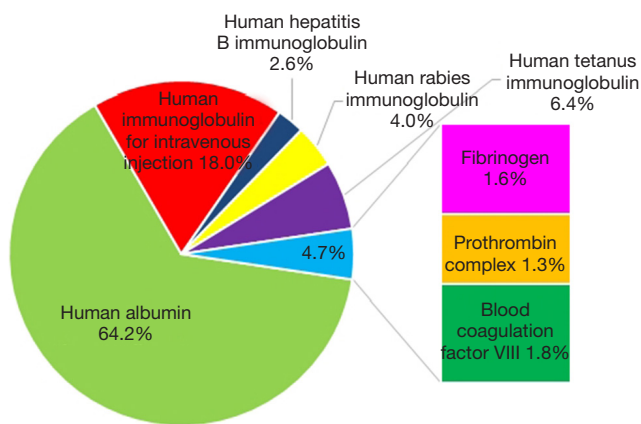


Figure 4 Proportion of plasma-derivations.

Table 2 Batch data statistics in 2016

Varieties	Batches
Human albumin	2,680
Human immunoglobulin for intravenous injection (pH 4)	711
Freeze-dried intravenous human immunoglobulin (pH 4)	13
Human normal immunoglobulin	36
Human rabies immunoglobulin	46
Human tetanus immunoglobulin	65
Human hepatitis B immunoglobulin	39
Human intravenous hepatitis B immunoglobulin	6
Freeze-dried intravenous hepatitis B immunoglobulin	1
Fibrinogen	169
Prothrombin complex	143
Blood coagulation factor VIII	129
Total	4,038

more than 100 fractionators subsequently sprung up all over China. However, the production capacity of most fractionators was extremely small, at less than 10,000 L per year. At that time, only 3 plasma derivatives (albumin (20%), intramuscular immunoglobulin (IMiG) and fibrinogen concentrate) were available in China. According to the *Regulations on the Administration of Blood Products* issued in 1996 (15), there are strict requirements to be met, including donor screening, automated (not manual) plasmapheresis, the storage of collected plasma, and product manufacture and distribution steps, etc. Since 1998, the development of the Chinese plasma fractionation industry has been on the

right track as a result of the implementation of the GMP principles in plasma product establishments to improve product quality, safety and supply. Meanwhile, the number of fractionators sharply declined from more than 100 to less than 30. Nowadays, the total designed production capacity (each batch of 2,500–5,000 L) is 12,000,000 L per year, however the total collected plasma is only approximately 7,000,000 L/year in China. More than 25 different protein products are available in developed countries, whereas only 12 plasma-derivatives can be extracted through large-scale fractionation of human plasma in China, including albumin, immunoglobulin (freeze-dried), hepatitis B immunoglobulin (freeze-dried), intravenous hepatitis B immunoglobulin (pH 4), intravenous hepatitis B immunoglobulin (pH 4, freeze-dried), IVIg, rabies immunoglobulin (freeze-dried), tetanus immunoglobulin (freeze-dried), coagulation factor VIII, fibrinogen, fibrin sealant and prothrombin complex.

China is one of the most important parts of the global market by both volume and value. Albumin assumes the largest proportion (*Figure 4*), with imported albumin taking more than a half. Consumers in China use albumin for volume replacement therapy. Albumin is also prescribed in China for other conditions such as kidney diseases, cirrhosis, cancer, and others.

According to data on blood products from the lot release system of eight biological products verification authorities of the China’s State Food and Drug Administration, a total of 4,038 batches were issued in 2016 (*Table 2*).

There were 3 kinds and 11 brands of plasma products in the Chinese Pharmacopoeia of 2015. The main product types and approval numbers of major plasma products facilities are shown in *Table 3*.

Future and challenges

Working together, great progress has been made in the Chinese plasma fractionation industry over the past 50 years. Both blood and plasma-derived products are regarded as strategic resources in China.

However, problems still remain. While millions of liters of plasma were collected annually with steady increases, self-sufficiency and strategic independence of plasma-derived products has nonetheless not yet been achieved. Clinical demand for plasma-derived products is increasing. Thousands of liters of plasma are discarded as unfit for fractionation, a loss that is both economically and morally inexcusable. Shortages of plasma for fractionation have become the “bottleneck” restricting the development of

Table 3 The main product types and approval numbers of major plasma products facilities

Product type	Hualan Biological	China National Biotec Group	Taibang Biological	Shuyang Pharmaceutical	Shanghai RAAS	Boya biopharmaceuticals
Albumin	√	√	√	√	√	√
Intravenous immunoglobulin	√	√	√	√	√	√
Freeze-dried intravenous immunoglobulin	√	√			√	√
Human immunoglobulin	√	√	√	√	√	√
Hepatitis B immunoglobulin	√	√	√	√	√	√
Intravenous hepatitis B immunoglobulin	√	√		√	√	
Rabies immunoglobulin	√	√	√	√	√	√
Tetanus immunoglobulin	√	√	√	√	√	
Factor VIII	√	√	√		√	
Human fibrinogen	√	√	√		√	√
Human prothrombin complex	√	√	√		√	

√, with approval number.

the Chinese plasma fractionation industry. In addition, Chinese plasma fractionators should enhance the research and development of new protein therapeutics to utilize the limited and valuable plasma sources as much as possible. The situation might change when a new edition of the *Regulations on the Administration of Blood Products* is issued so as to lead plasma fractionation industry development in a more rational and accelerated way.

With increasing domestic market demand, China keeps finding ways of communicating and collaborating with the international market. Contact between Chinese and foreign fractionators has been more and more frequent due to an open and free trade environment in China. The Chinese Innovation Union of plasma fractionators and collectors was established in 2017. Representatives of foreign fractionators were invited to participate in the communications and discussions. However, constructive dialogue between Chinese and foreign regulatory agencies (and fractionators) is still necessary and should be fostered in a regular and official way.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Thierry Burnouf) for the series “Plasma

Fractionation” published in *Annals of Blood*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob.2018.02.02>). The series “Plasma Fractionation” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the manuscript and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob.2018.02.02

Cite this article as: Wang Y, Wang Z, Liu B, Huang X, Li W, Li C. Plasma fractionation in China: progress and challenges. *Ann Blood* 2018;3:15.