Considerations on CMC Review for Blood Products

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II. Common problems in blood products

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I. Overview of blood products

Scope

- Biological products, such as human albumin, human immunoglobulin and human coagulation factors, are separated and purified from healthy human plasma or specific immune human plasma for diagnosis, treatment or passive immunoprophylaxis.
- It is defined basically the same as that by EMA, WHO and FDA.
- Animal immune serum products and animal-derived immunoglobulin products shall be managed as blood products.

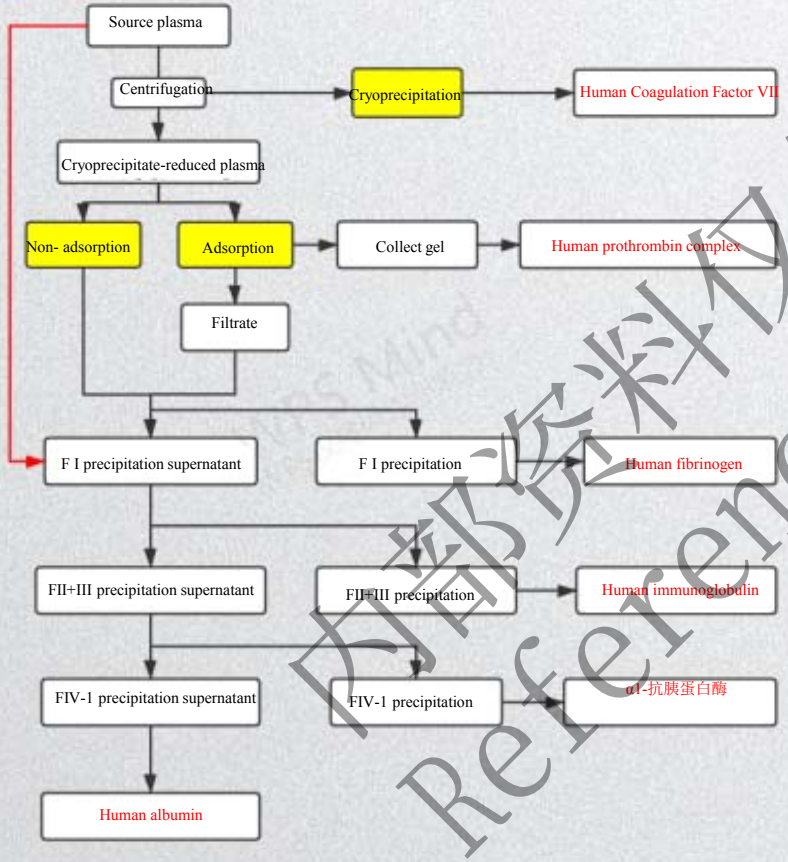
I. Overview of blood products

Basic characteristics

- Be derived from healthy human plasma
- Have potential virus risks
- Have complex molecular structure
- The biological analysis methods used for quality control, such as titer or bioactivity, are highly variable
- The State carries on the strict management: lot release by the State

I. Overview of blood products

Characteristics of production process



- More than 30 companies have production qualification for blood products
- The main blood products sold on the market include:

Human albumin

Human immunoglobulin (intramuscular)

Human Immunoglobulin (pH4) for Intravenous Injection

Human tetanus immunoglobulin

Human rabies immunoglobulin

Human Hepatitis B Immunoglobulin

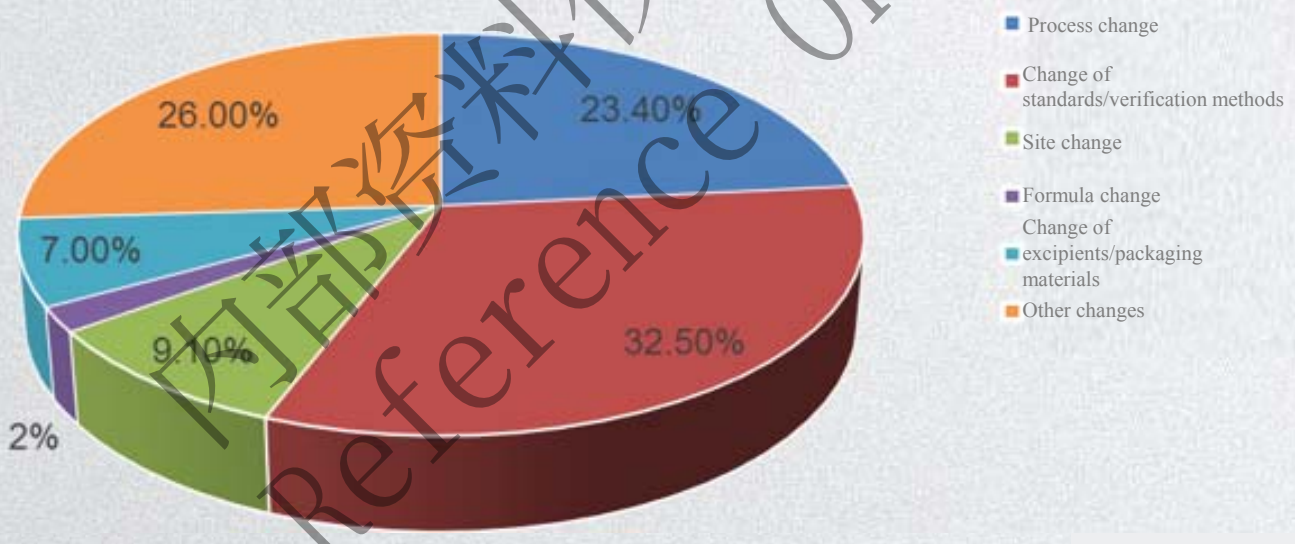
Human fibrinogen

Human prothrombin complex

Human coagulation factor VIII

I. Overview of blood products

In the past three years, the CDE has reviewed and approved about 150 supplementary applications of blood products (based on varieties), involving nearly 500 supplementary application items, most of which were site change, process optimization and standard improvement.



I. Overview of blood products

Relevant Guidelines

China: "Human Plasma for Production of Blood Products" in 2010 edition of Chinese Pharmacopoeia

Regulations on the Administration of Blood Products (Revised in 2016)

Appendix 4 Blood Products of Good Manufacturing Practice (GMP)

Technical Guidelines for Verification of Virus Inactivation/Removal in Blood Products

Technical Guidelines for CMC Study and Evaluation of Specific Human Immunoglobulin

Technical Guidelines for CMC Change Study of Marketed Biological Products (interim)

International: ICH related guidelines

Corresponding EMA, FDA and WHO guidelines may be referred to

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II. Common problems in blood products

1.Detection of source plasma

2.Verification of virus removal/inactivation

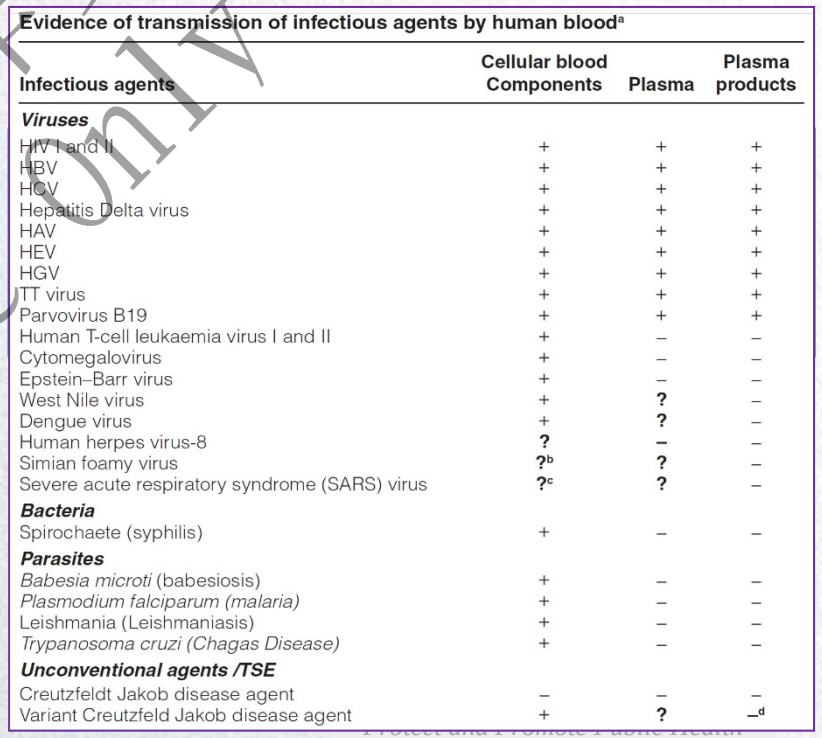
3.Post-marketing change

III. Summary

II. Common problems in blood products

1.Detection of source plasma

- Single plasma and combined plasma should all be verified;
- HBV, HCV, HIV-1, HIV-2, HTLV, B19, HEV, HAV
- An approved, more sensitive kit was used for verification
- Plasma samples should be retained, and retained samples should not be used for production
- Samples should be stored until 1 year after the expiry date of all the products produced by plasma

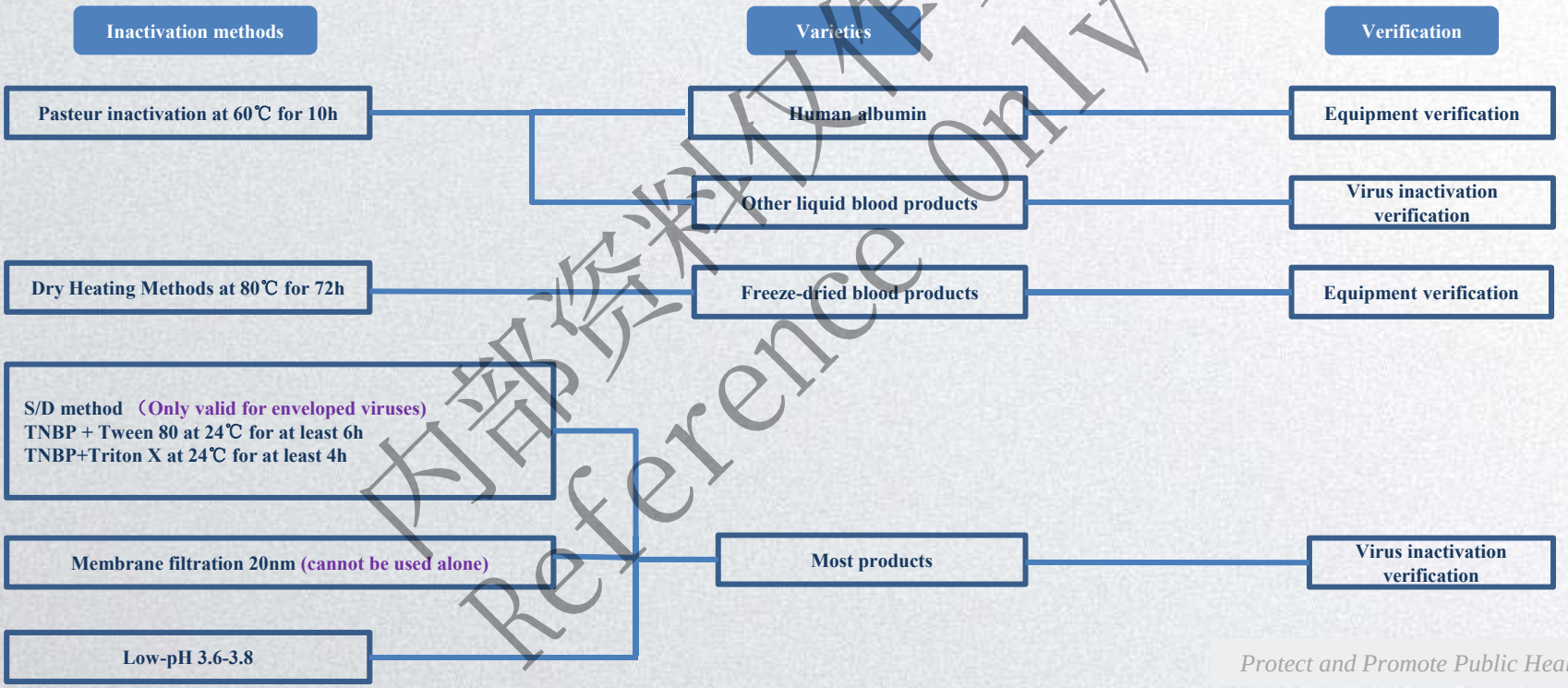


Evidence of transmission of infectious agents by human blood[a]

Infectious agents	Cellular blood Components	Plasma	Plasma products
Viruses			
HIV I and II	+	+	+
HBV	+	+	+
HCV	+	+	+
Hepatitis Delta virus	+	+	+
HAV	+	+	+
HEV	+	+	+
HGV	+	+	+
TT virus	+	+	+
Parvovirus B19	+	+	+
Human T-cell leukaemia virus I and II	+	–	–
Cytomegalovirus	+	–	–
Epstein–Barr virus	+	–	–
West Nile virus	+	?	–
Dengue virus	+	?	–
Human herpes virus-8	?	–	–
Simian foamy virus	?[b]	?	–
Severe acute respiratory syndrome (SARS) virus	?[c]	?	–
Bacteria			
Spirochaete (syphilis)	+	–	–
Parasites			
Babesia microti (babesiosis)	+	–	–
Plasmodium falciparum (malaria)	+	–	–
Leishmania (Leishmaniasis)	+	–	–
Trypanosoma cruzi (Chagas Disease)	+	–	–
Unconventional agents /TSE			
Creutzfeldt Jakob disease agent	–	–	–
Variant Creutzfeld Jakob disease agent	+	?	–[d]

II. Common problems in blood products

2.Verification of virus removal/inactivation



II. Common problems in blood products

2.Verification of virus removal/inactivation

Virus	Genome	Lipid envelope	Size（nm）	Examples of indicator virus
HIV	RNA	Yes	80~100	HIV
HBV	DNA	Yes	45	Duck hepatitis B virus and pseudorabies virus
HCV	RNA	Yes	40~60	Bovine diarrhea virus and Sindbis virus
HAV	RNA	No	27	HAV, poliovirus and encephalomyocarditis (EMC) virus
B19	DNA	No	20	Canine parvovirus and porcine parvovirus

研究病毒灭活动力学，包括病毒灭活速率和灭活曲线。

指示病毒滴度应该尽可能高(病毒滴度应≥10^6/ml)。

The volume ratio of the added virus to the sample to be verified should be no higher than 1:9.

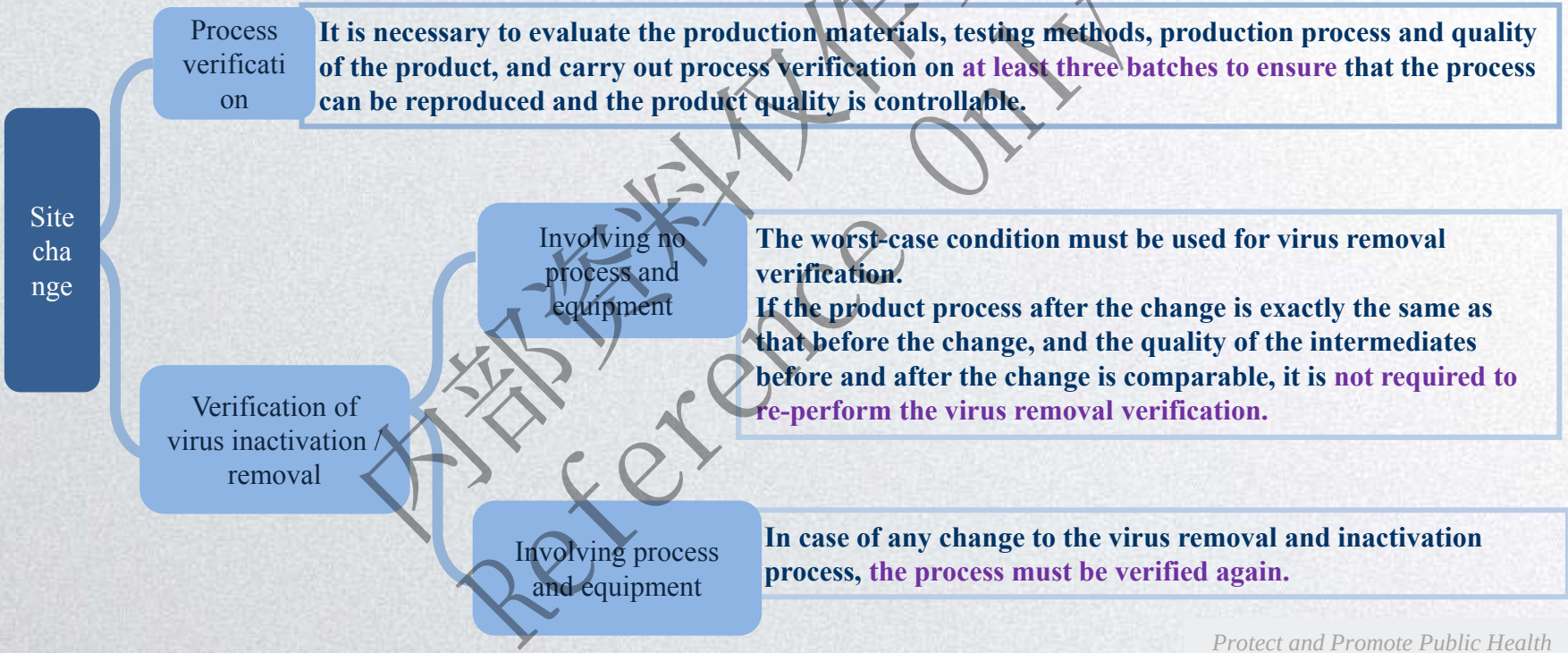
II. Common problems in blood products

2.Verification of virus removal/inactivation

- Coagulation factor products - There should be two or more virus inactivation/removal steps
- Immunoglobulins (including human immunoglobulin for intravenous injection, human immunoglobulins, and specific human immunoglobulins) - There should be specific methods for inactivating lipid-enveloped viruses, and it is recommended to add specific removal/inactivation methods for non-lipid-enveloped viruses in the manufacturing process.
- Albumin: Use low-temperature ethanol production process and specific virus removal/inactivation methods, such as Pasteur disinfection, etc.

II. Common problems in blood products

3.Post-marketing change



II. Common problems in blood products

3.Post-marketing change

Process change

① Cryoprecipitation— Increase the utilization rate of plasma

② Gel adsorption— Separate coagulation products and improve the utilization rate of plasma

③Chromatography step — increase purity and improve quality

Blood product enterprises are encouraged to add cryoprecipitation, gel adsorption and other process steps at upstream to increase the utilization rate of plasma by; Enterprises are encouraged to add chromatography steps to improve purity.

II. Common problems in blood products

3.Post-marketing change

Process change

Add cryoprecipitation and chromatography steps— Under the premise that relevant technical requirements are met, the production equipment, process and operation of commercial batch are all the same and the virus removal verification adopts the worst conditions, if a product with the same process procedure has been approved for registration and the virus inactivation/removal process has been verified, the virus removal/inactivation verification is not required again.

Add gel adsorption – Comprehensively judgment should be made based on the data submitted by applicants. If only this step is added and the addition of this step has no major impact on the product quality on the whole, the gel source does not introduce new safety risks, other process steps and their process parameters remain unchanged, and the quality of intermediates before and after the addition is comparable, the virus removal verification is not required again.

II. Common problems in blood products

3.Post-marketing change

Case 1

Application for process change of specific hepatitis B immunoglobulin products——
Plasma → separation → separation of each component → Component II→ Pasteur inactivation → purification → chromatography → low-pH incubation → ultrafiltration → bulk

- **Considering that the Pasteur inactivation process is the same as that of a specific human immunoglobulin of the company, and the inactivation verification of this step has been performed by the NIFDC at the time of approval of the specific human immunoglobulin, so repeated verification is not required.**
- **Considering that this product has the same low-pH incubation and inactivation conditions as the human immunoglobulin for intravenous injection of the company, and the inactivation verification by the NIFDC has been approved in the application of the human immunoglobulin for intravenous injection, so repeated verification is not required.**

II. Common problems in blood products

3.Post-marketing change

Case 2

Application for process change of human immunoglobulin for intravenous injection——

The approved process is: Precipitation dissolution → ultrafiltration → Pasteur inactivation (60℃ for 10h) → ultrafiltration → purification → ultrafiltration → sterilization and filtration→ low-pH inactivation → sterilization and filtration→ filling.

Proposed process for application: Precipitation dissolution –column purification→ ultrafiltration → Pasteur inactivation (65℃ for 9h) → ultrafiltration → ethanol purification → ultrafiltration → sterilization and filtration→ low-pH inactivation → sterilization and filtration→ filling.

- For major process changes, please carefully consider the impact on the quality and yield of intermediates;
- For Pasteur inactivation conditions, please provide the basis for the rationality;
- In case of significant difference between the proposed process and the approved process, it is recommended to verify the virus removal/inactivation process of this product again.

II. Common problems in blood products

3.Post-marketing change

Quality specifications	**Increase according to the Chinese Pharmacopoeia, the specification should be no lower than that of other similar products approved, adequate quality study of Al and IgA, statistical analysis on multiple batches of products, and development of reasonable quality indicators Principles: Advocate the improvement of quality specifications and sufficient methodological verification**
Verification methods	**Method selection: Methods in the Chinese Pharmacopoeia should be preferred. If self-developed method is selected, sufficient basis should be provided and full verification should be carried out According to the "Technical Guidelines for CMC of Marketed Biological Products (interim)", under normal circumstances, any change of verification methods or verification sites related to activity is a major change.**

II. Common problems in blood products

3.Post-marketing change

Stability	**Quality study and stability study of finished products produced by using intermediate products at the end of the validity period.** **Representative batch and reasonable packaging.** **Selection of quality study items: not only including the finished product release items, but also considering other quality-related factors. Bulk and preparations prepared with intermediate components from different process sources should be studied for quality specifications, such as the integrity of immunoglobulin, etc., which is related to the treatment methods of starting materials.** **In case of any change to the source of the plasma/cryoprecipitation, stability study should pay special attention to titer changes.**

II. Common problems in blood products

3.Post-marketing change

Validity period	**If a change item basically does not affect the quality and stability of the product, the changed product can obtain the same period of validity as the original product;** **If the change item may affect the quality and stability of the product, the corresponding period of validity shall be given strictly according to the support of the real-time long-term stability study data of the product after the change.**

Sufficient comparability study and data support

III. Summary

- Blood products enterprises are encouraged to improve the utilization rate of plasma; The process of blood products is relatively mature, and there are few innovative varieties.
- The contents of the application mostly focused on the application for post-marketing change;
- Pay attention to the safety, especially viral security;
- Post-marketing changes should be fully evaluated and verified.

Thanks for Listening