Technical guiding principles for pharmaceutical research and evaluation of specific human immunoglobulins

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I. Overview

Specific human immunoglobulin (Hyperimmune globulin, HIG)

It is a high-titer immunoglobulin prepared from plasma containing specific antibodies.

white preparation. Plasma sources include patients who have recovered from infection with a certain pathogen

High-titer antibody plasma and hyperimmune injections of healthy blood donors,

That is, injecting vaccines or other antigens to cause the recipient to produce antibodies, and then use apheresis to collect plasma

method to obtain plasma containing specific antibodies. Specific human immunoglobulin (in

(hereinafter referred to as: special immune products) because they contain high-potency specific antibodies, prevent

Immune globulin is more effective in treating specific diseases than ordinary people and is indispensable

of blood products.

In order to encourage, standardize and guide the research and development of specially exempted products, refer to domestic and foreign

Relevant technical requirements and combined with the actual domestic situation, this guiding principle is formulated. Book

The guiding principles are based solely on current technological developments and scientific understanding and are specific to exempt systems.

General technical requirements for pharmaceutical research proposed by the product. Applicants/holders may also submit

According to the actual situation of research and development of specially exempted products, other more effective methods and techniques should be adopted.

paragraph, but it should comply with the rules of drug research and development and provide scientific and reasonable basis.

Ensure the safety, effectiveness and controllable quality of products.

2. Scope of application

This guideline applies to methods that directly screen plasma donors for specific antibodies.

Obtained from formula and active immunization, produced with specific antibody plasma as raw material

Specially exempted products, they have similar product characteristics and pharmacological characteristics, and

The academic requirements have both commonalities and differences. The current Pharmacopoeia of the People's Republic of China

(hereinafter referred to as: "Chinese Pharmacopoeia") includes: hepatitis B patients

Immunoglobulin, rabies immunoglobulin, tetanus human immunoglobulin

etc. Please see Appendix 1 for the research and development and registration status of exempted products at home and abroad.

The methods are divided into intravenous injection, intramuscular injection, subcutaneous injection, etc.

3. General principles

1. Security

Due to the particularity of blood products, there is a potential risk of viral contamination.

Virus safety control is the core content of blood product quality control. Special free products

Collection, testing, storage, transportation, traceability of plasma and plasma donors

The immune requirements and other requirements must comply with the "human blood used in the production of blood products" in the Chinese Pharmacopoeia

"Plasma" and the "Quality Management Specifications for Plasma Apheresis Stations". It is recommended to

Carry out screening research on pathogens such as B19 based on product characteristics and clinical user groups, especially

They are some special varieties (such as anti-D immune globulin, etc.). Suggested Applicants/

The holder shall cooperate with relevant departments in conducting epidemiological surveillance in the area where the plasma station is located.

Actively promote raw plasma and mixed plasma nucleic acid detection technology, formulate standards and

Require. Special attention should be paid to the prevalence and detection methods of new and emerging infectious diseases.

Law.

2. Specific antibody screening

The accuracy and reliability of specific antibody screening results is to ensure the quality of raw plasma

key. In the case of large-scale production, the single plasma test involved

The amount is large, so it is necessary to establish a suitable antibody titer detection method in the early stage of research and development.

and fully validate the methodology. Single aliquots of plasma can be immunolabeled

method to carry out screening of specific antibodies and establish binding titer test results and neutralization

Correlation of potency test results. Combined plasma, stock solutions, and preparations should be

Methods specified in the "Chinese Pharmacopoeia" or verified methods for specific antibodies

detection. Usually virus neutralization test (mouse neutralization test, microcytosis

variable counting, plaque reduction test), immunolabeling test (enzyme labeling, fluorescent labeling

memory, isotope labeling, etc.), hemagglutination inhibition test, immunodiffusion test, immune

Based on turbidimetric test or other immunological/biochemical tests, the reference product is used as the standard.

Conduct research using quantitative and semi-quantitative methods.

3. Production technology

The process development of this type of product can refer to the process of similar products already on the market.

Platform technology can be used. Encourage the use of chromatography methods to improve product purity,

However, it is necessary to fully consider the impact of the selection of chromatography parameters and the quality of the chromatography resin on the product.

The impact on quality requires focusing on the ability of the process to inactivate and remove viruses.

Virus inactivation/removal verification should comply with the General Chapter "Biological Products Diseases" of the Chinese Pharmacopoeia.

"Virus Safety Control", "Technical Methods and Verification of Virus Removal/Inactivation from Blood Products"

Guiding Principles" and the requirements of technical documents such as ICH and WHO.

Establish a management system for personnel safety protection and waste during the production process

degree and operating procedures, and inactivate biologically active substances according to proven inactivation treatment methods

viruses, etc., and take effective protective measures to protect operators.

Avoid risks such as virus transmission.

4. Key points of pharmaceutical research and evaluation

(1) Raw plasma and materials used for production

1. Plasma source and quality control

Quality control of single plasma: Single plasma must comply with national health administration

Relevant quality control requirements issued by the department. The raw plasma used for production must be of appropriate quality

It has legal origin (certificating documents of pulp station, etc.) and has been inspected and quarantined. It should be complete.

Reagent information for blood-borne infection marker screening (marketing certification documents, etc.) and

Screening records (antigen/antibody/nucleic acid), etc.

Immunization program: The immunization program and the dose of antigen used are determined

Key factors for antibody concentration and titer in plasma. It is necessary to clarify the immunization method

, such as when using approved vaccines or other antigens for active immunization, these

Immunogens should have complete source certification information and batch information. Immunization program

The vaccine instructions should be referred to, or based on the immunogenicity of the antigen and plasma donors.

Reactive formulation, but the specific immunization schedule used needs to demonstrate safety. by

The examinee should have full right to know and at the same time formulate corresponding measures for possible problems that may arise.

countermeasure plan.

Quality control of mixed plasma: A certain amount of plasma must be mixed, and the combined product

Product characteristics should meet the requirements of the Chinese Pharmacopoeia. Currently, ordinary people are exempt from

The product requires the mixing of plasma from at least 1,000 plasma donors. Special free product one

Generally, it is required to mix the plasma of at least 100 plasma donors, and some special products

species (such as anti-D immune globulin products).

Whether active immunization with an approved vaccine or immunogen is used to obtain blood

Plasma, or plasma obtained after natural infection has recovered, both need to be submitted to the IND

At the time of declaration, specific antibody content standards for each plasma and pooled plasma shall be established.

Plasma whose antibody level test results meet this standard will be used for plasma production. for

Varieties not yet included in the "Chinese Pharmacopoeia", raw material plasma and specific substances in preparations

The titer of sexual antibodies should be established with a clear basis and a validated detection method.

For varieties that have been included in the "Chinese Pharmacopoeia", when applying for NDA, the antibody titer standard

It should not be lower than the requirements of each monograph in the Chinese Pharmacopoeia.

2. Raw materials for production

Strict quality control of the raw materials used in the production of special-free products is a way to reduce

Low risk of contamination by exogenous factors or toxic impurities in products, avoid other

Necessary measures for factor activation. Raw materials for production must have clear sources,

In addition to quality standards and inspection reports, we also need to focus on animal-derived raw materials.

(such as heparin, etc.), it is necessary to try to avoid the use of animal-derived raw materials.

Raw materials used in production should undergo a TSE/BSE risk assessment.

During the separation process, if filter aids (perlite, diatomaceous earth, etc.) and filter membranes are used,

When filter element materials are used, appropriate quality standards need to be established based on the requirements of different process stages.

control standards, control the risk of introduction of exogenous factors, and control bacterial endotoxins, severe

Metals are controlled and reasonable limit requirements are formulated. In addition, attention should be paid to the possibility

The risk of residues mixed into the final product and potentially harmful to the human body, if necessary,

its control.

(2) Production technology

1, undiluted solution

The starting raw materials of exempted products are raw plasma or plasma components, separated

Specific immunoglobulins mostly use the modified Cohn method or Kistler-

Nitschmann method, other methods can also be used for separation and purification, such as Xin

Acid precipitation method, chromatography method, etc.

The separation and purification process used should ensure better retention of the product.

Physicochemical and biological properties, retaining the biological activity of the Fc segment of IgG. production worker

Art must avoid or exclude microorganisms (bacteria, viruses) and their

Contamination of metabolites (pyrogen). Need to strengthen production process control and consider filter aids

The impact of agent removal, filter media selection, etc. on the product. Should pay attention to whether

IgG fractions obtained by different separation methods may contain higher levels of IgA

and IgM. At the same time, attention should be paid to the rationality of the sterilization and filtration steps, and

Inspection of filter membrane integrity after filtration.

It is necessary to clarify the investment of preclinical, clinical samples and marketing scale samples.

Pulp volume. Generally, production should be continuous, and the production capacity between each process step is mutually exclusive.

Match and complete processing in one go. In each process step, determine the work

Process control parameters and scope and compliance with requirements are the key to determining the quality of special-free products.

When using ethanol and other precipitation methods, the quality of ethanol and other reagents needs to be controlled.

system, and the protein concentration, temperature, pH value, ionic strength, processing time

Conduct research to clarify acceptable limits. Dissolution of plasma components and

During the precipitation process, avoiding co-precipitation of IgG is the key to improving product yield.

In particular, key indicators such as temperature and adding time should be fully studied and considered.

Observe the impact on key quality indicators such as protein purity and molecular size distribution.

When using chromatography methods, it needs to be based on the nature and concentration of the protein in the product.

Optimize chromatographic conditions and determine reasonable parameters, such as column capacity, feed liquid

And the ionic strength of the buffer solution and the pH value, flow rate and contact time of the buffer solution

and temperature, etc. The determination of these parameters should be based on the research data of process development.

basis, limit standards and allowable ranges should be formulated. At the same time, it is also necessary to analyze the chromatography tree

Grease cleaning, regeneration (service life), chromatography column loading, leachables, etc.

Conduct research, especially using chromatography media with potentially harmful ligands. Need to close

Note the volume, protein concentration, recovery rate, and electrophoresis of each separation and purification step.

Purity, etc., and evaluate the impact of process-related impurities (such as ethanol, precipitation aids, IgA, aluminum,

Removal performance of heavy metal ions, etc.) and product-related impurities (such as polymers, etc.)

force. When necessary, in order to prove the process's ability to remove impurities, it may be necessary to

Spiking tests should be used to evaluate the ability of the process to remove certain potential contaminants.

For example, operations involving temporary storage and transportation of intermediate products that may affect product quality

When necessary, it must be supported by necessary stability study data.

Encourage the adoption of innovative and improved processes, including improvements to ethanol separation processes

Advance), improve plasma utilization and improve the quality of specially exempted products. In the early process

During the development process, attention should be paid to the identification of key process parameters and attention to different separations

The integrity of stage process control and the rationality of process parameter settings. If applying

The owner/holder has products with the same separation and purification process on the market, and has process research and development

When research data, control parameters, etc. are available for reference, a 3-year study of new special-free products should be carried out.

Batch production scale process validation.

Considering the preciousness of plasma resources, pilot scale regulations suitable for clinical trials

Research data from the model can also be used for IND stage submissions. However, when filing an NDA,

Complete commercial-scale research data are required.

2. Preparations

Clarify single-serve prescriptions and batch prescriptions, and explain the basis for rationality of preparation prescriptions.

according to. Excipients that are suitable for medicinal purposes should be used and the stability of the supply chain should be ensured. for

Excipients from multiple suppliers require adequate research. For the country

Comprehensive research should be conducted on new excipients that have not yet been used in similar domestic and foreign preparations.

and report accordingly. Specially exempted intravenous injection products must not contain any bacteriostatic agents. because

Certain sources of co-solvents (e.g. polysorbate 80) have the potential to cause allergic reactions

and the risk of hemolytic reaction, safety evaluation should be conducted.

The formulation preparation process (such as stirring speed, etc.) should be studied.

In principle, the preparation of the product should come from a batch of original solution, and different batches of original solution can be prepared together in one batch.

For finished products, possible risks should be assessed. Dealing with product issues during the packaging process

temperature, duration of dispensing, temperature and humidity of the dispensing environment, etc.

system. Specially exempted products involving freeze-drying processes should be commercialized batch-verified

Freeze-drying process parameters, freeze-drying curves and other data illustrate the impact of the freeze-drying process on product quality.

Quantity, especially the impact on biological activity and other aspects.

3. Process verification

For intramuscular injection special-exempt products, the process flow needs to be determined before NDA filing.

process and key process parameters, and continuously produced three batches of products to verify the stability of the process.

Provide supporting evidence for product launch. For special-exempt products for intravenous injection, you should

Determine the process flow and key process parameters before confirmatory clinical trials, and continuously

Continue to produce 3 batches to verify the stability of the process. If clinical trial samples and commercial regulations

There are differences in the production process or site of the mold batches, and it is recommended to make changes.

Research, it is recommended to carry out research and exploration of the worst process conditions at the appropriate stage,

It is necessary to prove that under the determined process parameters and quality control limits, it can produce

Produce qualified products. If multiple production sites or production lines are involved, all should be carried out

Validation studies.

(3) Virus safety and virus removal/inactivation verification

The detection of single plasma and mixed plasma should comply with the requirements of the Chinese Pharmacopoeia

Please note that the number of mixed slurries should meet the sensitivity requirements of the kit/detection method. right

For anti-D immune globulin, production of pooled plasma B19 viral nucleic acid vectors should be ensured.

Amount <104 IU/ml.

Due to the ability of various methods to inactivate/remove lipid enveloped and non-enveloped viruses,

differences, it is recommended to use two virus inactivation/removal methods with different mechanisms to conduct experiments.

Certificate, clarify the technical conditions and control parameters of the virus inactivation/removal process steps,

Including product uniformity, upper and lower temperature limits, inactivation time, filtration pressure/speed

degree/temperature/solution composition/membrane integrity, etc. Attention should be paid to the inactivation/removal process steps

The rationality of the location setting. When selecting a virus removal/inactivation method, address

The effectiveness of inactivating/removing viruses is balanced against product activity, general safety, etc.

consider.

Potential interactions between inactivation steps and inactivation process antagonisms need to be considered.

body integrity and its impact on clinical efficacy, whether new immunogens are formed,

and the risk of toxic residues that may be introduced. If the production process changes,

If the virus removal ability may be affected, re-verification is required. Additionally, for

The samples tested should be representative of the process. With the advancement of technology, some new

The virus inactivation method can also be used in specially exempted products, and the method used must be proven.

The law is scientifically valid and fully verified.

If a product with the same process steps has already been approved and registered and has been tested for virus

For inactivation/removal process verification, the newly declared product only changes the administration method, and the commercial

The production equipment, processes, operations, etc. of the industrial batch are all the same as the original product.

Products that comply with the "Technical Methods and Verification of Virus Removal/Inactivation from Blood Products"

Guiding Principles", "Technical Guiding Principles for Pharmaceutical Change Research on Marketed Biological Products"

Subject to relevant technical requirements, virus inactivation/removal may not be repeated.

Process Validation.

To ensure the viral safety of the final product, epidemiological data should be considered

Station setting, strict selection of plasma donors, plasma screening and quarantine period management, optimization

The production process and the addition of virus removal/inactivation steps, and the overall process of producing products

Evaluate the viral clearance capabilities of the process steps. Evaluate production processes for inactivation/removal

Viral capacity versus the maximum load of a particular virus that may be present in the initial plasma,

To maximize the virus security of your product, ensure that verification includes the worst-case scenarios

Condition.

(4) Quality research and control

1. Analysis of physical and chemical properties

It is necessary to combine the product type, preparation type and drug development stage, and gradually

Further improve the analysis of physical and chemical properties. Based on preliminary research data on physical and chemical properties,

When filing IND and NDA filings, comparative studies on physical and chemical properties should be conducted.

Including antibody integrity, antibody subclass distribution, circular dichroism analysis, etc.

2. Biological activity

Biological activity studies should be fully carried out, and it is recommended that binding potency and neutralization

Potency detection methods were used to conduct correlation studies. From the perspective of supporting the rationality of the process, consider

Considering the impact of the process on the product, etc., it is recommended to establish Fc biological function testing

Method, it is recommended to conduct research on the sialic acid content of the Fc segment during the development stage. Production

Process, antibody titer, IgG aggregates, IgG subclasses, etc. will all affect the response to Fc

biological function test results. In addition, it is recommended to carry out Fc segment and immune cell

Surface receptor binding ability, Fc segment activation of complement function, and opsonophagocytosis

Wait for analysis.

3. Purity and impurities

It is necessary to pay attention to the components that have an impact on the functions of this type of product. The purity is generally not low.

At 95%. In addition to conducting research on impurity residues and proving the impurity removal capabilities of the process

In addition, different stages of batches should also be set appropriately (if there are clinical and commercial regulations

model batch) impurity level limits. It is recommended to use highly sensitive methods to control impurities

Protein content.

Polymers and anti-complement activity produced during the preparation of special immune products

(ACA), emphasis should be placed on controlling the IgG multimer content. To prevent congenital

If patients with sexual IgA deficiency cause severe allergic reactions after using special immune products, the IgA content

should be controlled. Specially immunized intravenous products should be used against anti-A and anti-B hemagglutinins

Conduct studies on equal amounts and establish limit standards to prevent possible

Can cause hemolytic reaction. Encourage testing of coagulation activator levels and recommend

Establish standards. It is recommended that anti-D be carried out for intravenous special immune products derived from special plasma.

Antibody testing. In addition, in order to prevent the risk of thrombosis, it is recommended that intravenous injections be specially prepared

Control the FXIa content of products and establish standards.

Encourage research on detecting other impurity proteins in blood, such as kallikrein

Zymogen activator, immunoglobulin M, transferrin, albumin, ÿ1-antitrypsin

Protease, ÿ2-macroglobulin, haptoglobin, ÿ1-acid glycoprotein, copper

Cyanin, fibrinogen, antithrombin III, plasminogen, fibrin

Vitiligo, C1 esterase inhibitor, etc.

Specially exempted products, especially intravenous injection products, need to focus on the treatment of insoluble

Control of sexual particles. Insoluble particles cannot be metabolized in the human body and remain in the microorganisms.

Thrombosis can easily be induced in small blood vessels. Aluminum content should be controlled, aluminum

There are potential risks to the central nervous system, bones, and other organs that

The risk is related to the dose infused.

4. Quality analysis and standards

Specially exempted products that have been marketed should comply with the requirements of the Chinese Pharmacopoeia. New

Specially exempted products must fully consider the rationality of the setting of testing items. should be based on different

Characteristics of drug delivery products and reasonable setting of quality standards, such as special exemptions for intravenous injections

Products should be tested for FXIa factor, aluminum ions, IgA content, etc.

When filing an IND, special attention should be paid to relevant aspects such as antibody titer and harmful residues.

related test items.

When filing an NDA, it should be based on the data from each research and development stage and stability investigation.

Based on the statistical analysis of multiple batches and combined with the requirements of the "Chinese Pharmacopoeia"

and similar products, reasonably formulate the raw liquid, semi-finished products (if any) and preparation

quality standards for pharmaceuticals, focusing on quality control of potency, and encouraging the establishment of more stringent internal

control standards. The titer detection method should use advanced and mature methods, and encourage the use of

A variety of complementary analytical methods are used for quality control in the early stages of research and development. In preparation

If excipients such as maltose, polysorbate 80, and glycine are added, the quality of the preparation should be

Control it in the quantity standard and clarify its content range.

5. Analytical methods and methodology validation

Combined with product characteristics, select reasonable analysis methods and conduct adequate

Legal verification to ensure the feasibility of the method.

When filing an IND, at least preliminary antibody titers and harmful residues should be completed

Validation of physical detection methods.

When filing an NDA, the establishment and verification of complete analytical methods should be completed.

Clarify the accuracy and precision of the measurement method (including repeatability, intermediate precision

and reproducibility), specificity, limit of detection, limit of quantification, linearity, range and tolerance

usability and other indicators. Methods other than those in the Chinese Pharmacopoeia should be applied for

Conduct comprehensive methodological validation when submitting an NDA. If comparing measurement methods

When major changes are made, the scope of revalidation should be determined based on the degree of method revision.

Establishment and validation of antibody titer detection methods: production should be carried out before research and development

Product-specific antibody titer determination methods and standard studies. Recommended for binding potency

Conduct correlation studies with neutralization potency detection methods. Try to use "Chinese Medicine"

"Chinese Pharmacopoeia" methods, for those not included in "Chinese Pharmacopoeia", try to choose classic,

Has an industry standard approach. Clarify the test operation procedures, test parameters, work

Prepare and calibrate standards and determine results. Based on antibody titer detection

The method itself selects appropriate indicators to conduct methodological verification and establishes a verification plan.

In general, in terms of linearity, the correlation coefficient of the neutralization potency determination method should be consistent with the expected

Acceptance standards are set first. In terms of accuracy, the actual measured dilution times

The ratio between the neutralizing antibody titer of several sera and the theoretical titer is 1, or

The slopes of regression lines in analysis of variance are parallel. In terms of precision, variation

The coefficient should be controlled within 30% as much as possible. In terms of durability, cell density needs to be examined

Degree (generation), neutralizing virus dose, neutralization reaction conditions and time, well plate

The influence of different positions, etc. on the test results. Can be exposed to strong light, high temperature, high

Accelerate the destruction of the test sample by wet and other methods to study possible degradation.

Impact of products and degradation pathways on potency determination. Encourage the use of working standards

Conduct quality control to reduce test interference factors and improve the accuracy and reliability of results.

Validation of hazardous residue detection methods: Usually, hazardous residues are at trace levels

Quantity level, the sensitivity of the detection method determines the reliability of the results. Encourage in

Based on the method of "Chinese Pharmacopoeia", more advanced methods and sensitivity are adopted.

For higher instruments and equipment, pay attention to distinguishing between instrument detection limit and method detection limit. get

The obtained detection limit and quantitation limit data must be verified with samples with similar contents.

Describe the test process and detection limit results, including accuracy and precision verification numbers

according to. Linear indicators such as recovery rate (%) and relative standard deviation (RSD%)

The standard should list the regression equation, correlation coefficient, residual sum of squares linear plot, etc.

The range should be drawn up to be within ±20% of the specified limit based on preliminary actual measurement data.

In general, a variety of methods with different principles should be used for mutual verification.

Methodological verification of product-related impurities: combined with the requirements of the "Chinese Pharmacopoeia"

Carry out methodological validation. If commercial kits are used for residue detection,

It is recommended to conduct research on detection kit selection (such as IgA detection), detection reagents

The box should state the sensitivity, specificity, limit of detection, limit of quantitation, and linear range

and other indicators. Under normal circumstances, the accuracy, precision, line quality of the test kit should be

Conduct performance verification on indicators such as sexual range, interference test, reference interval, etc. Precision

The coefficient of variation of the accuracy should be within 20%, and the accuracy deviation should not exceed 10%.

The coefficient of determination (R 2) of the sexual range is ÿ0.98, and the relative deviation of the interference test should be less than

10%. Attention should be paid to identifying factors that may affect the measurement results during product release testing.

Accuracy factors, such as pH value, PK activity, product solution ionic strength,

Reaction temperature, etc. will affect the measurement results of PKA. Low pH conditions may cause

The PKA activity of the product is reduced.

6. Reference products (standard products)

Antibody titer quality control reference materials should be established in accordance with the requirements of relevant guidelines.

When filing an NDA, it is necessary to clarify key information such as the source and quality control of the reference product.

The test products should be related to the samples used in clinical experiments, and attention should be paid to the accuracy and traceability of the assignment.

source. If international/national standards are used, the information on the standards used should be clear.

(source, batch, etc.). If it is a self-made reference product, the preparation process and standardization should be carried out.

stability, stability and other related research.

(5) Stability research

Stability testing runs throughout the entire product life cycle and is an important part of formulating product standards.

accuracy and validity period. Should follow the "Chinese Pharmacopoeia" and domestic and foreign biopharmaceuticals

Conduct stability tests in accordance with relevant guidelines for product stability research. Notification in IND

stage, a preliminary stability investigation can be carried out to ensure the stability of clinical stage samples.

quality. Complete a comprehensive stability investigation before NDA filing and select the appropriate

Packaging materials, clear storage and transportation conditions, and establish a reasonable validity period.

Inspections such as influencing factor tests and accelerated tests should be conducted as far as possible into the product

Until unqualified. Long-term stability inspection should extend the observation period of the product as much as possible

between. Generally speaking, liquid dosage forms should be placed upside down or upright.

Carry out stability test according to the situation. Products with different closed systems should be stabilized separately.

Qualitative testing.

If a new production location is introduced to produce intermediate products, unless otherwise

For other reasons, stability studies on intermediate products and stability of finished products should be implemented

Research. Fc segment activity is an important indicator of the effectiveness of this type of product, and it is recommended to

Related stability investigation. For specially exempted products in liquid dosage form, heat stabilization should be carried out

Qualitative test and inspection of visible foreign matter, the results should comply with the "Chinese Pharmacopoeia"

Require.

(6) Packaging and sealing container systems

The source and control standards of inner packaging materials should be clarified, and

Technical Guidelines for Research on Compatibility of Injections and Pharmaceutical Glass Packaging Containers (Trial Industry)", "Technical Guidelines for Research on Compatibility of Chemical Injections and Plastic Packaging Materials" Guiding Principles (Trial)" and other relevant guiding principles as well as the requirements of relevant ICH guidelines Please conduct research on packaging material compatibility and sealing properties. leachable, dissolution, shedding Objects, etc. should comply with the limit requirements. Pay attention to the leaching of inner packaging materials, rubber stoppers and glass bottles Effects on formulations.

5. Explanation of terms

1. Blood Products: refers to products derived from human blood or blood Plasma therapeutic products, such as human albumin, human immunoglobulin, human coagulation factor Zi et al.

2. Human Normal Immunoglobulin Immunoglobulin (HNIG): also known as gamma globulin or multivalent immune globulin Protein is obtained by using low-temperature ethanol protein separation method or other approved protein separation methods. Immunoglobulin preparations isolated from healthy human plasma, including Intravenous human immunoglobulin, intramuscular human immunoglobulin and subcutaneous human immunoglobulin Globulin etc.

3. Specific human immunoglobulin (Hyperimmune globulin, HIG): It is a high-potency immune system prepared from plasma containing specific antibodies. Immunoglobulin preparations. Plasma sources include patients recovering from infection with a certain pathogen of plasma with high titers of antibodies, and hyperimmunization of healthy blood donors Injection, that is, injecting vaccines or other antigens to cause the recipient to produce antibodies. Plasma containing specific antibodies is obtained by plasma collection. with ordinary immunoglobulin

Different, such preparations must have at least one high-titer antibody for clinical use prevention and treatment of specific diseases.

4. Anti-complement Activity (ACA):

One type present in serum or tissue fluid can non-specifically bind to complement, causing Its inactive substances, such as proteases, esters, etc.

6. References

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Appendix 1: R&D and registration status of specific human immunoglobulin products at home and abroad

Foreign	domestic
hepatitis B human immunoglobulin (IM/IV) Hepatitis B human immunoglobulin (IM/IV)	
Rabies immune globulin Rabies immune globulin (IM)	
Tetanus Human Immunoglobulin (IM/IV) Tetanus Human Immunoglobulin (IM)	
Intravenous injection of cytomegalovirus human immunoglobulin Intravenous injection of cytomegalovirus human immunoglobulin (clinical)	
Anti-Rh (D) human immunoglobulin (IM/IV) Anthrax immunoglobulin (clinical)	
Botulinum toxin human immunoglobulin	SARS-IVIG (National Stockpile)
Varicella-zoster virus (VZV) human immunoglobulin Protein (IM/IV)	Intravenous COVID-19 human immune globulin (clinical)
Respiratory syncytial virus immunoglobulin	
rubella human immunoglobulin	
measles human immunoglobulin	
Hepatitis A human immunoglobulin	
anthrax immune globulin	
vaccinia human immunoglobulin	