免疫细胞治疗产品药学研究与评价技术指导原则（试行）

Drug Evaluation Center of the State Drug Administration

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Table of contents

I. Introduction..... 1

2. Scope of application..... 1

3. General principles..... 2

(1) Research and development rules..... 3

(2) Technical considerations related to product features..... 5

4. Risk Assessment and Control..... 7

Five ,Production materials..... .....9 (1) Raw

materials..... 9

(2) Excipients..... 16

(3) Consumables..... 16

6. Production process..... 16

(1) Process research..... 17

(2) Process control..... .....twenty two

(3) Process verification..... .....twenty three

7. Quality research and quality control..... .....twenty four

(1) Quality research..... .....twenty four

(2) Quality control..... .....29 8. Stability

research..... ....34 (1) Basic

principles and storage stability research..... .....34 (2) Research on

transportation stability..... 35

(3) Stability study in use..... .....36 (4) Storage condition

labeling..... ....36 9. Packaging and

sealed container system ....37 10.

References..... 38

I. Introduction

In recent years, biotechnology has developed rapidly, promoting immune cell therapy products
The research and development has provided new treatments for some serious and refractory diseases.
In 2017, the former State Food and Drug Administration issued the “Cell Therapy Products
"Technical Guiding Principles for Drug Research and Evaluation (Trial)", which provides guidance on the
An overall review of the pharmaceutical technical requirements for research and declaration of cell therapy products was conducted.
Elaborate. Due to the cell sources, types, in vitro
There are large differences in operations and other aspects, and quality research and quality control are more complex than traditional drugs.
Adding complexity to standardize and guide immune cell therapy products in accordance with Good Drug Administration
Conducted research and development and evaluation to develop these guidelines.

This guideline is based solely on current scientific understanding and is not specific to immune cell therapy.
It puts forward general technical principles and suggestions for pharmaceutical research on drugs, and the content is not mandatory.
sex. The applicant/holder may also adopt other effective methods based on the specific circumstances of the product.
conduct research and explain the rationale. With the development of technology and deepening understanding of
With the accumulation of experience, the technical requirements for related products will be gradually revised and improved.

2. Scope of application

In this guideline, immune cell therapy products refer to products derived from the human body (autologous/allogeneic
Somatic) cells or cells of human origin cell lines, which have been manipulated in vitro, including but not limited to
Used for isolation, purification, culture, amplification, induced differentiation, activation, genetic modification,
Establishment of cell banks (lines), cryopreservation and recovery, etc., and then injecting or implanting them into patients
Internally, the immune system treats diseases by inducing, enhancing or suppressing the body's immune function.
Immune cell therapy products, such as chimeric antigen receptor T cells (Chimeric

Antigen Receptor T-Cell (CAR-T), dendritic cells (Dendritic

Cell, DC) etc.

Somatic cells such as islet cells and chondrocytes, as well as cellular and non-cellular components

The cellular portion of the combination product may also refer to this guidance. cell derived products

products, such as cell exosomes, cell lysates, inactivated cells and other products, whose cells

Some pharmaceutical studies may also apply. For genetically modified immune cell therapy

For therapeutic products (such as CAR-T, etc.), the cell part can refer to this guideline.

For genetic modification, please refer to other relevant technical guidelines. This guideline does not apply to

For stem cells, hematopoietic stem cells for transfusion or transplantation, germ cells, and

Tissue-like products and organoid products composed of cells.

This guiding principle applies to research and development and

Registered immune cell therapy products are mainly suitable for those in the marketing application stage.

Pharmaceutical research.

3. General principles

Immune cell therapy products developed and declared in accordance with the requirements of the Chinese

Drug Administration Law of the People's Republic of China", "Measures for the Administration of Drug Registration", "People's Republic of China

Pharmacopoeia of the Republic of China (referred to as "Chinese Pharmacopoeia") and other relevant laws and regulations.

The production process of immune cell therapy products should comply with the "Drug Production Quality Management

Specification (GMP) basic principles and related requirements. biosafety

In this regard, it should comply with relevant national laws and regulations. Human tissues, cells, genes

The source and processing should comply with the relevant national laws and regulations on the management of human genetic resources.

regulatory requirements.

(1) Research and development rules

Pharmaceutical research on immune cell therapy products follows general rules for drug development laws throughout the entire life cycle of the product. This type of product has strong personalization and high craftsmanship It is complex and diverse, sensitive to the environment, has a short validity period in the non-frozen state, and is delicate at the same time. The cells themselves have the ability to survive in the body, autonomous proliferation and/or differentiation, and cell-cell interactions. and other capabilities, its pharmaceutical research should fully consider the above basic characteristics and special characteristics of the product. While meeting the technical requirements at different stages, pharmaceutical research needs to continuously optimize ization and improvement to improve product quality.

1. Apply for clinical trial stage

The pharmaceutical technical requirements for applying for the clinical trial stage must be combined with the product's own Characteristics and production process specific conditions for overall evaluation and judgment. To protect Subject safety, clinical trial applications usually focus on safety-related aspects, such as quality control of raw materials used in production, reduction of mix-ups/contamination/cross-contamination measures for contamination risks, process stability, safety-related critical quality attributes, Non-clinical research samples/non-registered clinical research samples (if applicable) and clinical trials Quality comparability of samples, etc. In addition, the production conditions of clinical trial samples should comply with Comply with the basic principles of GMP.

Under normal circumstances, the following studies need to be completed when applying for clinical trials: Raw materials and excipients used in the production process, especially materials of human origin/animal origin, Carry out adequate safety analysis and evaluate the necessity and rationality of use. Production The process needs to undergo transformation research and evaluation from laboratory processes to processes for clinical trials. Determine the steps and parameters of the cell production process that are suitable for the clinical trial stage,

and production process control measures, etc., to support the rationality and stability of the process, and to Sufficient to meet the production capacity needs of clinical trial samples and ensure product safety and quality Quantity controllability. Complete safety-related quality studies, such as exogenous factors, impurities quality, etc., and complete relevant methodological confirmation. Quality control aspects, setting and clinical Quality standards suitable for the trial phase and safety-related quality control can be combined with Quality research can also refer to existing safety standards or consensus standards for similar products. In addition, comparative analysis of non-clinical research and non-registration clinical trials is required (if applicable) and clinical trial production processes (broadly including raw materials, sites, production processes technology, scale, etc.) and sample quality. If necessary, conduct risk assessment and Deep research. Declaration of clinical trial stage, stability of storage, transportation and use The stability study conditions should be representative, and the stability study data should be able to support clinical samples. actual storage conditions of the product. Materials that come into direct contact with the sample must undergo safety and Assessment of suitability.

2. Application for listing stage

Based on sufficient process development and research, establish a mature and stable business Chemical production technology can continuously and stably produce safe, effective and quality-controllable products. product. The commercial production process should undergo comprehensive process verification and production should be strictly controlled. The quality of production materials, clarify key production steps, key process parameter ranges, Critical process control items and acceptance criteria. After thorough quality research, Legal verification and stability research to establish reasonable quality standards. according to specifications Stability research and packaging material compatibility research, formulating product validity period, clarifying transportation, Conditions and duration of use, and identification of appropriate packaging containers/materials.

3. Process changes

Applicants/holders are encouraged to continuously improve and optimize production processes and continuously improve product quality. If a process change occurs, corresponding feasibility checks should be carried out based on the change. Comparative study, analyzing the comparability of product quality before and after the change to prove the change It will not have any adverse impact on the safety, effectiveness and quality controllability of the product.

(2) Technical considerations related to product features

1. Raw materials for production

The raw materials used in the production of immune cell therapy products come from diverse and different sources. Risk assessment should be carried out in accordance with the relevant requirements of the Chinese Pharmacopoeia and quality control, and establish a good and standardized quality management system for raw materials used in production. Tie. Prioritize the use of raw materials with high quality standards or low risk levels. Conduct biosafety assessment and control of raw materials of human origin/animal origin to reduce external sources Risk of introduction or spread of agents.

Cells used in the production of immune cell therapy products can be of autologous origin or allogeneic Source, source of human cell lines, etc. Reasonable procedures need to be established when cell/tissue collection is involved Clear medical institution quality assessment content, review and screening principles and standards. Applicants/holders are advised to conduct quality assessment, review and screening of collaborating medical institutions selection, ensure the regulation of the collection process by establishing and using collection operation files, etc. Norm. In addition, based on quality research, donor screening standards and systems need to be established. Determine the quality requirements for collected cells/tissues, and regulate the storage and storage of cells/tissues after collection. Establish clear operating specifications for processes such as transportation and factory inspection.

2. Production process

The production process of immune cell therapy products is complex, without virus clearance and terminal destruction.

Bacteria step, its production should follow the principles and requirements of GMP, and the production process has

Validate and establish clear process controls. Particular attention should be paid to personnel, plant and equipment,

Raw material control, environment and facilities, etc. The overall zoning layout of the production plant should comply with

management, each area should be reasonably designed and laid out according to the process steps and corresponding cleanliness levels.

The bureau and operation and maintenance can meet the quality management requirements for the production of immune cell therapy products.

It is recommended to use automated, continuous, closed or semi-closed production equipment as much as possible,

Use dedicated, product-specific devices that meet the requirements to control contamination risks,

Minimize the risk of contamination by microorganisms and various particles. Create opening and clearing

On-site system, establish a whole process control system to avoid using raw materials and production operations

External contamination or cross-contamination that may be introduced during operation. during production process,

Attention should be paid to the operating time and spatial isolation of batches of cells from different donors to avoid different

Confusion and cross-contamination of batch samples. Establish a product traceability management system,

To ensure the traceability of products from donor to recipient.

3. Quality control

Quality control strategies for immune cell therapy products include material quality control,

Production process control, intermediate sample quality inspection, final product release inspection and

and sample inspection, etc. In principle, each batch of products must pass quality control and inspection

Released after passing the test. However, considering the particularity of immune cell therapy products, in

On the premise of controlling the risk to the greatest extent, it can be combined with the emergency degree and production of clinical use.

Develop reasonable and flexible quality control policies based on the methods/time of product storage and transportation, etc.

slightly.

4. Storage and transportation

The storage and transportation process of immune cell therapy products may involve freezing or refrigeration, storage and transportation conditions, time, and corresponding packaging should be Passed verification. For frozen products, attention should be paid to the impact of freezing and thawing on product quality. The quality of Suhou's products should meet the requirements for clinical use. For fresh food that does not need to be frozen Products, storage and transportation conditions and times must not only ensure product quality, but also require Meet the timeliness requirements for clinical use.

4. Risk Assessment and Control

Immune cell therapy products are characterized by diversity, heterogeneity, and complexity. Different types of products may carry different levels of risk. Therefore, it is necessary to characteristics of the product, from raw materials, production process, product quality control, stability, clinical Conduct a comprehensive risk assessment using multiple factors including the application process. Please refer to ICH Q9 risk management concepts, scientific use of risk assessment tools, and identify, analyze and evaluate risk factors, and make plans based on the risk assessment results Establish corresponding risk control measures. Risk assessment and control throughout product production life cycle, it is necessary to continuously analyze risks as research deepens and product knowledge accumulates. Factors are tracked, analyzed and updated, and data are collected to further determine their risk characteristics. Collect and formulate corresponding control strategies.

According to the current product research status, the pharmaceutical aspects of immune cell therapy products Risk factors may come from the following categories:

(1) Source of cells (such as autologous/allogeneic, human cell lines, etc.), Acquisition method, type and biological characteristics (such as proliferation, differentiation, migration ability,

The ability of cells to function themselves, secrete active substances, initiate/enhance/suppress immune responses

force, etc.).

(2) Safety risks of materials, such as the use of raw materials of human origin/animal origin

use.

(3) Cell production process, such as equipment openness/sealing, production process

Possible mix-ups, internal and external contamination/cross-contamination; degree of manipulation of cells,

Such as in vitro culture/amplification/activation/induction/gene modification/frozen storage/resuscitation/transportation, etc.;

The extent to which the operation affects cell characteristics, such as the effect of genetic modification on cell function

wait.

(4) Quality research and quality control, existing research and inspection methods or methods

Whether the method can adequately characterize the characteristics of the product and control the quality of the product, such as biological

Activity and purity studies (such as non-target cell populations, impurity residues, non-cell formation

points) etc. Whether the detection method and detection indicators are applicable, and verify the new detection method

Whether it is sufficient, for example, whether the new test method is equivalent to the pharmacopoeial method, whether the new

Rapid detection methods have the risk of false negative or false positive results, etc.

(5) Storage, transportation conditions and time of cells for production and final cell products,

The sealing and compatibility of storage containers, etc.

(6) Form a group with non-cellular materials (bioactive molecules or structural materials)

Combined products, etc.

Other types of risk factors may include: Mode of administration (e.g., systemic

injection, topical application or surgical application); different conditions of the recipient (such as whether

To pretreat the recipient, the type, stage, severity or progression of the disease

speed, etc.) on product quality, production cycle, storage method or transportation time

Requirements; past experience with similar products or the drawability of relevant experience, etc.

5. Production materials

Production materials refer to the materials used in the production process of immune cell therapy products.

The sources of all raw materials, auxiliary materials, consumables, etc. should be clear and the quality should be guaranteed.

Certification, special attention should be paid to preventing the introduction or spread of exogenous agents. material suppliers and

Contract manufacturers need to be evaluated, audited, and, if necessary, signed into a quality agreement

Control quality risks in other ways.

(1) Raw materials

Raw materials are directly related to the quality of the product and should be produced in accordance with the "Chinese Pharmacopoeia"

Conduct risk assessment in accordance with the requirements of "Quality Control of Raw Materials and Excipients for the Production of Articles"

evaluation and quality control, and establish a good and standardized raw material quality management system. base

Based on the characteristics of immune cell therapy products and their production processes, it is recommended that

Try to use raw materials that meet pharmacopoeia standards or have been approved for human use, otherwise

Raw materials with high quality standards and low risk levels should be used as much as possible and ensure

its safety and suitability. Raw materials include starting materials (e.g. production cells,

Production of helper cells, in vitro genetic modification systems) and other raw materials (e.g. culture

base, added factors, other biochemical reagents, etc.).

1. Starting raw materials

1.1 Cells for production

According to the current development of biotechnology, the sources of cells for production include human donors.

sources (autologous cells, allogeneic cells) and human cell lines. for

The source of patient cells should comply with relevant national laws, regulations and ethical requirements, and Establish a "knowledge and confidentiality" management system. Cell lines should have clear origins and passage history The history is clear and security risks are controllable.

1.1.1 Donor-derived production cells

Donor screening:

In order to ensure product quality and the biosafety of the production environment and production personnel, Safety, based on research, product risks and donor cell use needs, a contract needs to be established. reasonable donor screening procedures and standards, and try to collect relevant characteristics of donors, including Including but not limited to age, gender, previous known medication and radiation exposure, Stay in epidemic areas, past medical history, family history, pathogenic microorganism screening information, HLA (human leukocyte antigen) typing information, blood type, and routine blood tests Test etc. The criteria for donor screening vary depending on product characteristics, but they need to be set appropriately and Ability to control corresponding risks.

In terms of pathogenic microorganism screening, allogeneic donors should at least meet the national requirements Regulations regarding blood donation, such as screening donors for the presence of human immunodeficiency virus (Human immunodeficiency virus, HIV), hepatitis B virus (Hepatitis B virus, HBV), Hepatitis C virus (Hepatitis C virus, HCV), Treponema pallidum and other infections. According to the actual situation of the product, additional Corresponding testing items, for some specific products, have clear risks and clear Those who require viral testing need to be tested, such as donors of T cell therapy products In addition to the above-mentioned pathogenic microorganisms, it is also recommended to perform human cytomegalovirus (Human Cytomegalovirus) cytomegalovirus (HCMV), human Epstein-Barr virus, human T lymphocytes

Virus (Human T-cell Leukemia Virus, HTLV) screening. self

Donors also need to carry out corresponding pathogenic microbial screening to ensure that the production process and

Product use will not cause contamination or add additional risks to patients themselves.

Depending on the specific circumstances of the donor's health/disease history or stay in the epidemic area, it may also be adapted.

Add corresponding screening items and establish acceptance standards and procedures. To make sure

To ensure the sensitivity of the detection method and the reliability of the detection results, it is recommended to use regulated

Agency-approved kits are used, and blood source screening kits are given priority to detect pathogenic microorganisms.

biology. Allogeneic donors also need to consider the impact of the window period on pathogenic microorganism screening.

ring.

In addition to pathogenic microorganism detection, additional tests can be added based on clinical use and production needs.

Additional screening programs for donors, e.g. for products of allogeneic origin, are recommended

When appropriate, evaluation includes typing of polymorphisms, such as blood group, primary relationship between donor and recipient

To match histocompatibility antigens (class I and/or class II HLA), in some cases

In this case, it may be necessary to pay attention to minor histocompatibility antigens and clarify and establish typing procedures.

and standards.

Cell/tissue acquisition, processing and examination:

In order to ensure that the quality of donor cells meets production requirements, the cells/group responsible for

Conduct evaluation and review of medical institutions where tissue collection is collected, and select medical institutions with relevant qualifications.

The medical institution serves as the institution for donor cell/tissue acquisition and establishes the name of the cooperative medical institution.

order, formulate corresponding cell collection operating specifications, and encourage the signing of relevant quality agreements

At the same time, medical institutions regularly collect donor cells/tissues and clinical application cells.

Review, analyze and evaluate the quality of the final product.

Cell/tissue harvesting procedures need to be fully studied. According to product characteristics

Based on the research, determine the cell or tissue source, collection method and other relevant

Identification information, including but not limited to collection site/environmental requirements, equipment used and

Procedure, reagents and consumables used, blood collection volume, etc. Cell/tissue acquisition including apheresis

Blood collection, peripheral blood collection, lymphoid tissue separation, umbilical cord blood collection, tumor group

Various collection methods such as tissue separation are recommended. It is recommended to consider the cell type and donor health.

conditions and cell requirements, etc., give priority to collection methods that are easy to operate in a standardized manner.

Such as blood component apheresis technology, etc. Methods of obtaining cells/tissues need to be studied

and demonstrations, including but not limited to types of enzymes, anticoagulants, blood analysis equipment, and

Procedure (circulating blood volume, flow rate, etc.), surgical method, etc. Minimize as much as possible during collection

Related impurities, such as cell debris, non-purpose cell content, etc., and consider reducing the

The degree of damage inflicted on the donor's tissues and organs. avoid unnecessary or inappropriate

Processing and handling steps to avoid damaging the integrity and/or function of cells and thereby

Reduce the risk of adverse reactions or treatment failure. Doctors who collect cells/tissues

Service personnel must undergo strict training and obtain corresponding qualifications and authorizations before they can take up their posts.

Operations and training should be recorded. The environment in which collection operations are performed should ensure that the collection

Microbiological safety of cells/tissues. During the collection process, microbial contamination and sample

Control the risk of product cross-contamination or mix-up.

If the collected cells/tissues require further processing, such as mixing, batching,

Packaging, storage, transportation, etc., need to carry out corresponding research and verification work, and based on

Determine appropriate storage conditions, transportation methods and time based on the research situation, and formulate relevant

The operation should be standardized.

When the collected cells/tissues enter the factory, they need to be inspected for appearance, packaging integrity, etc. inspection, and confirmation of transportation temperature, time, and donor information.

Before production, cell types and numbers can be determined based on process requirements, product characteristics, etc. Detection of quantity, phenotype, viability and microorganisms, etc., such as cell type can be Identification and confirmation through relevant genotypic and/or phenotypic markers, and the markers are positive The specific cell ratio can be used as a basis for the evaluation of expected cell population indicators. Encourage research Study cell/tissue quality indicators related to finished product quality and include collected cells/tissues Organizational quality release standards.

1.1.2 Production cells derived from cell lines

Immune cell therapy products derived from human cell lines, the cell lines used It should meet the requirements of clear source, clear generation history, comprehensive and qualified test results, etc. beg. In principle, a cell bank should be established for cell lines and managed hierarchically for use in production. The level of the cell bank can be based on the characteristics of the cells themselves, production conditions and clinical needs. Comprehensive consideration of clinical application conditions; and refer to the "Chinese Pharmacopoeia", ICH Q5A, ICH Q5D and other relevant requirements establish inspection standards for cell banks, and the inspection results should meet the requirements. beg. Cell lines may be genetically modified for production, and if possible, it is recommended Construct and test the genetically modified cell lines.

1.1.3 Storage of cells for production

It is recommended to establish or adopt a stable and controllable cell storage system or platform, and research Determine appropriate storage conditions and packaging materials for donor cells or cell lines When the characteristics of cells change, the cells should be properly preserved to ensure that they have been stored properly.

The risk of microbial contamination is not increased during the process, and the viability, density, and purity of the cells are and biological functions to meet production requirements.

1.2 Production of helper cells

Depending on the purpose or function, production helper cells may be viral packaging cells, Feeder cells, etc. Production of helper cells should be consistent with the source and Clear culture passage history, controllable safety risks, and hierarchical cell bank management (if applicable), basic principles for qualified inspection results. Produce helper cells if needed To expand culture, it is recommended to complete the expansion of final production auxiliary cells at one time as much as possible culture, or ensure the consistency of culture process and quality for each expansion, and evaluate the expansion Whether new risks are introduced during the large-scale cultivation process. If applicable, it is recommended to create a different Inspection procedures for production steps/stages, such as inspection time, inspection items, inspection methods laws and acceptance criteria, etc. Attention needs to be paid to its species-specific virus detection and possible Incoming security risks. Processes involving trophoblast inactivation treatments such as irradiation or Adding drugs, etc., should be researched and verified.

1.3 Gene modification system

If genetic modification is involved, please refer to the relevant technical guidelines for the genetic modification system. South, I won't go into details in this article.

2. Other raw materials

The collection, sorting, culture and genetic modification of cells A variety of materials are also required, such as culture media, enzymes, antibodies, cytokines, serum, antibiotics, magnetic beads, other chemicals, or solid supports such as gels matrix), etc., the use of these materials may affect the performance of immune cell therapy products

quality. Its risk assessment content includes the source, components, functions, use of raw materials
Use stage, quality control, etc. Relevant documents required include certificate of source,
Inspection report (COA), instructions, TSE/BSE-free statement, etc. to prove
It is fit for purpose and suitable for its intended use. Based on the risk profile, the
The production process can refer to the relevant principles or requirements of GMP.

If antigens need to be used in the production process, they must meet the requirements of clear source, risk and quality.
Controllable quantity requirements. Recombinantly expressed or synthesized antigens require clear selection criteria, anti-
original sequence, production process-related risk factors and quality control, and identify the antigen
Impurity control (including exogenous viral factors, etc.). tumor cell lysate
Antigens need to pay attention to the stability and quality-related risks of the production process, such as tumorigenicity or
Contamination from external factors, etc. Antigen residues in immune cell therapy products need to be fully evaluated
Possible immune-related risks, etc.

Try to avoid using potentially allergenic materials during production, such as ÿ-
Lactam antibiotics (such as penicillin), etc. Try to avoid using raw materials of animal origin
Materials, such as animal serum and animal-derived proteins, should be used with clear ingredients as much as possible.
alternatives of non-animal derived materials. If raw materials of animal origin must be used, it is required
Carry out corresponding research to prove the necessity and rationality of its use, according to the raw materials
Establish a complete quality control system based on the species origin, production area, production process and other characteristics.
system, assess TSE/BSE safety risks, and conduct analysis on residues of animal-derived raw materials.
Conduct testing and conduct safety risk assessments. It is strictly prohibited to use animal blood from epidemic areas
Serum/plasma should not be used without safety verification. If produced
The process of using autologous serum or autologous plasma requires the development of serum/plasma production technology,

Research on quality, stability, packaging, storage, etc. During the production process, try to avoid non-

The use of allogeneic human blood-derived materials for medicinal purposes, if necessary, needs to be based on risks.

You can refer to the relevant requirements of blood products to carry out exogenous factor contamination, effectiveness

and batch-to-batch consistency, combined with the manufacturer's release testing standard system

Set reasonable internal control standards.

(2) Excipients

For excipients, please see the "Preparation Formula and Process" section in the "Production Process" chapter.

(3) Consumables

Disposable consumables such as culture bottles, pipelines, and filters used in the production process,

Culture and packaging containers, production equipment and materials in contact with intermediate samples, etc.

After rigorous screening, suitability and biosafety assessments were conducted, and based on the

Carry out corresponding compatibility studies based on the evaluation results.

Immune cell therapy products may be combined with other medical devices, matrices, microcapsules, etc.

Materials form combined products. Cell sections can refer to this guideline. overall group

Combined products need to examine and evaluate the interactions and risks of cells, devices and other materials.

6. Production process

The production process within immune cell therapy product manufacturing plants often includes

from cell/tissue receipt or cell line initiation to final cell harvest, preparation,

The whole process of storage and transportation to the factory. The overall production process needs to be fully studied

and verification to determine stable and feasible commercial production processes, including but not limited to

Cell receipt, cryopreservation of collected cells (if applicable), in vitro manipulation, preparation,

Product freezing, etc. The determined production process includes reasonable process operation steps and parameters

numbers, production process control and acceptance standards, etc. The entire production process needs to be monitored

Control, including monitoring of process parameters and process control indicators. Combination product production

Process research and validation also includes the combination of individual components to form the final combined product.

All process steps of the product to ensure the feasibility and stability of the production process.

(1) Process research

With the deepening of research, the production process needs to be continuously optimized. Construction of process research

It is recommended to use cells/tissues that are consistent with the actual source and quality of production to carry out research.

If cell quantities are limited (e.g., autologous cell products), consider using similar

Characteristic, representative, and sufficient number of cells for study.

1. Production capacity and batch definition

The production capacity of immune cell therapy products directly affects the acceptable

The number of patients treated, the number of treatments and the quality of the product are determined by cell characteristics,

Production process, factory buildings, personnel, facilities and equipment, clinical use and other factors determine

Certainly. The formulation of production capacity needs to be verified by research. From laboratory preparation to

In the stage of industrial production transformation, we need to pay attention to the way of expanding production capacity and carry out research and development.

Research to ensure product quality. If in the study of production capacity expansion, always maintain production

The production process remains unchanged and the batch production volume of each batch of products remains unchanged, but by increasing the production batch

When expanding production capacity in multiple ways, we need to focus on raw materials, personnel, public

Verification of facilities, equipment, production environment and quality control and inspection to

Ensure that capacity expansion will not affect product quality. If production capacity is expanded

In large-scale research, new production processes have been introduced, such as the use of multi-layer cell factories or

or cell reactors and other equipment, it is necessary to focus on the possible impact of changing the process on quality.

impact and carry out corresponding comparability studies or assessments.

The purpose of defining batches is to ensure uniform quality of immune cell therapy products and traceability. Products of the same batch should be from the same source and of uniform quality. After sampling inspection according to the regulations, the quality of the entire batch of products can be evaluated. because The processes of immune cell therapy products are diverse and complex, and can be manufactured based on the characteristics of the product process. determine the applicable batch definition. According to the existing product technology, immune cell therapy Product batches can be considered to be defined as: in the same production cycle, using the same production Process, a certain number of products of uniform quality produced under the same production conditions for a batch. The total amount of all cells produced in a single batch is the production of batch size.

2. Production process development

The process development of immune cell therapy products needs to be based on the quality profile of the target product. Combined with physical and chemical properties and biological characteristics, rationally design experiments, continuously optimize, and gradually Step by step to establish a stable production process and key process parameters. For target product quality Overview research requires product characteristics from multiple aspects, such as surface markers, cell Viability, purity, biological activity, target gene transduction efficiency, etc. are analyzed. and initially obtain critical qualities that may affect product safety and effectiveness. Attributes. Determine critical processes based on their impact on critical quality attributes parameters, and establish matching parameter ranges. With the deepening of process research and experience Continuous optimization through accumulation of experience. Possible key process parameters include but are not limited to: Starting cell number, culture medium composition, cell expansion, induction, genetic modification operations Make relevant process parameters, etc.

When developing the cell culture process in vitro, the conditions for cell growth in vitro need to be considered.
components and the impact of any manipulations that may have on the cells to maintain cell integrity and functionality
performance characteristics. The steps of the operation (medium replacement, passage, activation, genetic modification, induction
guide, etc.), added ingredients (culture medium, recombinant proteins and related growth factors,
Serum substitutes, magnetic beads, viral vectors, nucleic acid materials, transduction/transfection reagents
etc.), culture container, culture conditions (such as temperature, dissolved oxygen, pH, etc.), impurities
Removal, culture time or maximum number of passages, culture scale and parameter settings are all
Corresponding research and verification should be carried out. To monitor cell quality, it is recommended
Establish detection methods and standards to continuously monitor the characteristics of cells during the production process,
Such as changes in genotype and/or phenotype and function of cells after cell culture expansion
etc. to determine or optimize the production process.

If the cell culture medium is not a liquid medium but a non-liquid matrix
/Instruments/stents (top) and other culture media need to consider their effects on cell growth and function.
and integrity effects, such as the cellular environment that degradable biomaterials may cause
changes (such as changes in pH value, ion concentration, gas-liquid interface, etc.), and should also
Consider the effects that cells may have on the culture medium (e.g., degradation rate, medium shape
state, medium composition, etc.).

If there is an operation to induce cells in vitro, the induction methods and conditions need to be
Conduct studies that incorporate changes in cell growth characteristics, cell phenotype and/or genotype
changes in cell function, residues of inducing substances, target cell populations and
The changes in the proportion of non-target cell populations are studied and verified, and continuously optimized.

If there is an operation to genetically modify cells in vitro, the method of operation (such as electroporation, viral vector transduction, etc.) and conditions, such as selection of pro-transduction/transfection reagents Selection, transduction equipment (such as electroporation apparatus), virus multiplicity of infection (MOI) and other conditions Conduct research and combine the transduction/transfection efficiency of the target gene and the Integration status in chromosomes, target gene expression stability, cell genotype and /or changes in phenotype, function, residue and removal of risk genes such as carcinogenesis, disease Research on the process of virus replication ability, reverse mutation, insertion mutation or insertion site, etc. research, optimization and verification.

3ÿ Preparation formula and process

The overall goal of formulation research is to ensure that the dosage form and prescription are reasonable and the process is stable, Effectively control the production process and suitable for industrial production. In research, based on the product itself Determine the dosage form, preparation formula and prescription process of the product based on its characteristics and clinical application. art. Formulation studies generally include:

(1) Selection of dosage form

Immune cell therapy products are generally injections. If using other dosage forms, Reasonable selection should be based on clinical usage.

(2) Prescription research

Based on the characteristics and stability research results of immune cell therapy products, the results Characteristics, usage and route of administration of the mixture, rational design of trials, and prescription screening selection and optimization, and finalize the prescription. Prescription research mainly focuses on specifications, excipient ingredients Distribution, dosage, usage, and product handling during storage, transportation, use, etc. Stability performance, etc. Preparation prescriptions should be adapted to storage conditions. Immune cell therapy

Therapeutic products often involve refrigeration and/or freezing. studies, cell cryopreservation and/or
The impact of freezing conditions and time on cell characteristics and viability status to determine the production
drug prescription. Non-frozen immune cell therapy products generally have shorter storage times;
Preparation formulas should be able to meet the requirements for stable product quality during storage, transportation and use.
Require.

The use, dosage and quality of excipients should be studied and verified to prove
Necessity, safety and rationality of its use. Preferably medicinal or approved
Excipients intended for use in humans otherwise require comprehensive research and evaluation. for new
type of excipients, in addition to the above studies, it is recommended to conduct appropriate non-clinical safety studies
For details, please refer to the relevant technical guidelines that have been released. Frozen free
Cryoprotectants are commonly used in immune cell therapy products, which are mainly divided into penetrating cryoprotectants.
Protective agents (such as dimethyl sulfoxide (DMSO), glycerin, ethylene glycol, etc.) and non-penetrating
Sexual cryoprotectants (such as polyvinylpyrrolidone, albumin, sucrose, trehalose
wait). Factors that may be considered when selecting a cell cryoprotectant: Cell Freezing
The toxicity and immunogenicity of the protective agent itself (such as DMSO, albumin, etc.)
influence on cell properties, function and stability, removal methods or acceptable residue levels
Standards, freezing equipment and procedures, quality and origin of cell cryoprotectants
Source, ingredients, dosage, usage, etc. Cell cryoprotectants should be validated in studies
(such as DMSO, etc.) composition, dosage and rationality. Combined with selected freezing
Protective agent, if the product needs to undergo physical state change,
Operations such as filtration, cleaning, container conversion, dosage adjustment, combination with other materials, etc.
It should be fully researched and verified.

(3) Preparation process research

Based on the characteristics and stability research results of immune cell therapy products,

Combined with production conditions and equipment, conduct process research and verification to determine preparation production

processes and establish appropriate process control standards. Preparation process studies can be conducted separately

Yes, it can also be done in conjunction with prescription research. Formulation process studies need to be considered

Prevention and control of risks of confusion and contamination, materials (containers) that come into contact with the preparation process

The adsorption or effect on cells, the impact of shear force generated by filling on cells, etc.

At the same time, ensure that the cell number and density meet the requirements.

(2) Process control

Good process control is key to ensuring product quality. Properly set up production

Sampling time points, test items and standards or related process parameters for process control

Output standards to ensure the stability of product production processes and products between different batches

Consistency of quality. For closed cell culture systems, the closed system

Structure, sampling process and other characteristics should be used to arrange process control sampling operations as appropriate to prevent

pollute.

Establish a reasonable process control strategy based on product and production process characteristics, and establish

It is recommended to pay attention to the following aspects: (1) Monitor sample mix-up and cross-contamination, including

Donor materials, intermediate samples and products in the production process, paying special attention to different suppliers

or cell line-derived cell manipulations should be effectively isolated in time/space; each

The site needs to be cleared after production, using proven standard procedures for cleaning and

Disinfection. Before each production operation, confirm the clearance situation. (2) Supervisor

Control contamination by microorganisms and their metabolites/derivatives (e.g. endotoxins), if applicable

It is recommended that sterility, mycoplasma, etc. be carried out on suitable intermediate samples at critical time points.

Safety-related testing or taking relevant measures to control. (3) Monitor the production process

key process parameters or key quality attributes in the process, such as cell viability, proliferation ability

strength, cell phenotype, impurity content, biological activity, etc. Quality supervision during the process

Control and release testing can be combined and complementary to each other. (4) Ensure samples of the entire production process

and production materials (including from cell/tissue collection process, production, transportation to clinical

Traceability throughout the application process).

(3) Process verification

The process validation of immune cell therapy products can follow the process validation of biological products

According to the general principle, each operating unit and intermediate sample of the production process have been determined.

product storage conditions and time, media/buffer preparation and storage conditions, transportation

Cheng et al. conducted process verification. Process verification should be able to prove that the production process complies with regulations

Process parameters that can consistently produce products that meet the intended use and registration requirements

Goods.

In compliance with ethics and informed consent, it is recommended to use

Carry out corresponding research on cells similar to clinical application scenarios (such as patient-derived cells)

Research; with sufficient process research, autologous cell therapy products or other

For products with restricted cell sources, consideration may also be given to using products that are considered effective after research and evaluation

Representative healthy donor cells are used for relevant process validation and are also considered in

Carry out simultaneous verification after listing.

In the verification work, attention should be paid to the research and development of the maximum production capacity at the same stage at the same time.

Verification, the actual maximum production capacity shall not exceed the verified maximum production capacity, production

Increases in performance require appropriate validation. Raw materials, excipients, personnel,

Facilities and equipment, environment, quality inspection capabilities, overall operation capabilities, etc.

Support capabilities for large production capacity, considering verification of worst-case conditions. Complete commercialization

After the production process is verified, continuous process research and verification are required to ensure that the process

in a controlled state.

7. Quality research and quality control

(1) Quality research

Quality research is process optimization and improvement, formulation of overall control strategies and assurance

The foundation of product quality runs through the entire life cycle of the product. Comprehensive quality research

Research is conducive to the determination of critical quality attributes, and it needs to be deepened and understood with the deepening of product understanding.

The development of technology is constantly supplemented and improved. Quality research requires the use of corresponding research phases

(e.g. non-clinical research batches, clinical trial batches, commercial production batches) or

Appropriate steps (such as donor cells or cell line cells, in-process samples, or

representative sample of finished product).

Quality research on immune cell therapy products generally includes safety research, purity

Research on purity and impurities, functional research, research on other projects, etc. can also be based on

The product's own characteristics add other related research.

1. Safety research

Mainly includes microbial safety research and safety related to the product itself

Research. The former refers to microbial contamination and microbial metabolite/derivative contamination.

research, such as fungi, bacteria, mycoplasma, viruses, endotoxins, etc.; the latter is

Refers to matters that may cause safety problems to the product itself in addition to microbiological safety.

Related research, such as malignant transformation of cells, non-target cell residues, etc. According to cells

The types, characteristics and sources, production processes and related material characteristics are compared with the above two aspects.

comprehensive safety research. It is recommended to include at least the following aspects (if applicable):

Exogenous factors: production cells, production auxiliary cells, other human/animal sources

Exogenous factors may be introduced into raw materials and during the production process. in progress

On the basis of routine detection of exogenous factors, based on the possible introduction of exogenous factors,

Detect specific exogenous factors using a combination of in vivo and in vitro methods. For example, produce

If bovine serum is used, detection of specific bovine-derived viruses is required; if porcine pancreas is used

enzyme, it is necessary to detect pig-derived specific viruses; if trophoblast cells are used, it is necessary to

Detection of cell species-specific viruses. For allogeneic therapeutic products, prescribing

When conducting human-derived virus testing, attention should be paid to the possibility that the donor is in the infection window period, and appropriate

Secondary sampling and testing will be carried out.

Replication competent virus (RCV): RCV

Generation through viral vector reverse mutation is an important test related to product safety.

Test items need to be studied through applicable testing methods.

Malignant transformation of cells: In some cases, the cells in the product have become malignant

The possibility of transformation (including but not limited to tumorigenicity, pro/tumorigenicity, etc.). here

In this case, it can be determined based on the source of immune cells and the characteristics of the target cells in the product.

or residual impurities and other factors, combined with in vivo and in vitro experiments, adverse effects on cells

The possibility of sexual transformation is studied and evaluated.

Gene insertion site and copy number: Because it is related to product safety and

Effectiveness needs to be studied using applicable testing methods to explore its relationship with safety

correlation with efficacy.

Abnormal immune response: It is recommended to choose appropriate ones for cell products derived from allogeneic sources

Methods for immunological reaction detection.

Unintended Cells and Impurities Research: See below for details.

2. Purity and impurity studies

The quality and biological activity of immune cell therapy products often differ from those in the product.

Depends on the purity of the target cells. The actual situation may be more complicated: on the one hand, no

Products of the same type have different purity requirements for target cells; on the other hand, the same

The impact of different cell populations or subpopulations in a type of product on the biological activity of the product

Also different, the proportion of cells in different cell populations or subpopulations needs to be studied. cell

Purity studies may include, but are not limited to:

Proportion of viable cells: Applicable methods need to be used to study the proportion of viable cells.

Research. When the immune cell therapy product is a single cell type and is homogeneous,

The purity of a product can be studied by directly measuring the proportion of viable cells in the product.

Cell population or subpopulation ratio: When immune cell therapy products are of many different types

type or a mixture of cells of different genotypes/phenotypes, it is recommended to study samples

The composition of cells in a cell, such as the composition and proportion of cell populations or subpopulations. For example, root

According to the mature stage (naive, senescent, exhausted, etc.), the immune cell group or subgroup

research.

Proportion of target cells: Products can be studied by detecting the proportion of target cells of purity. For example, in CAR-T products, after the CAR transfer operation is performed, Finally, the target cell population for purity analysis should be selected to correctly express both CAR and The target cells for T cell surface markers cannot include T cells that do not express CAR. cells and cells that express CAR but have incorrect T cell surface markers.

Proportion of non-purpose cells: Non-purpose cells may have adverse effects on product quality. Therefore, cell purity studies should also include the characterization of non-target cells. and/or quantitative research. For example, residues of non-target cells such as tumor cells and iPS cells has a higher safety risk and therefore needs to be studied proportionately and carried out Strict controls. After research, when non-target cells have a negative impact on product safety and effectiveness If there is no impact, its composition and proportion need to be studied, and if necessary, the batch-to-batch variation should be controlled. Consistency.

Impurities:

Process-related impurities: refers to impurities introduced during the process, such as residual proteins Enzymes, induction reagents, transduction/transfection reagents, serum, viral vectors, and residues The remaining magnetic beads, fibers, plastic microbodies, trophoblasts, etc. need to be removed using appropriate methods. method to conduct research.

Product-related impurities: such as non-target cells, products expressed unexpectedly by cells, Dead cell residues, cell debris and other possible degradation products need to be treated with appropriate methods used for research.

For high-risk impurity ingredients that may be present in the product, information should be established and clearly understood. Accurate removal methods and residual quantitative detection methods, if the impurity components cannot be effectively removed

otherwise, safety and toxicity should be assessed in animal models or other systems,

and set residues based on the maximum human exposure dose or in vivo safety study results.

limit.

3. Functional research

Functional research is to evaluate immune cells through in vivo/external functional analysis experiments.

Research on whether cell therapy products have the expected biological functions. According to cell production

the nature, characteristics and intended uses (indications) of the product, especially to achieve clinical treatment

specific mechanisms and indicators of the effect, and establish and verify appropriate in vivo/external functional analysis

Analytical methods and carry out functional research. Its functional studies may include, but are not limited to

The following aspects:

Differentiation/development potential: can cover the possible differentiation/development methods of cells in the product

Towards. Among them, differentiation/developmental functions related to clinical application safety and effectiveness

It is recommended to be included in quality control as representative evaluation content.

Qualitative and quantitative studies of expression products: When immune cell therapy products function

When the expression of endogenous or exogenous gene products is involved, research on the expression products should be carried out.

research, such as the type, characteristics, expression level, modification degree (such as

Glycosylation, phosphorylation, etc.), polymerization (such as homologous or heterologous polymers, etc.), etc.

Response to exogenous stimulation: related factors can be studied on the effects of factors on cells after birth

Cellular reactions, such as changes in cell morphology, changes in cell proliferation ability,

Cytokine secretion, phenotypic changes, signaling pathway changes, metabolic changes

Wait.

Biological activity: According to the product characteristics and mechanism of action, carry out detailed research on the product body

Study biological activities corresponding to expected functions, such as effects on target cells (e.g., lytic decomposition reaction, induction of apoptosis or proliferation), secretion of specific factors, etc. If born Stimulation by adding ingredients during the production process (such as induction, antigen loading, etc.), or Obtain functions after genetic modification (such as gene editing, exogenous gene expression, etc.) cells, it is necessary to carry out applicable biological activities on the cells before and after stimulation or operation. Sexual research, comparative analysis of cell function before and after stimulation or operation. Dangzhi When the subsequent research experiments are limited by the number of cells required or other conditions, it can be developed and implementation of reasonable alternative testing methods.

4. Research on other projects

In terms of physical and chemical properties, the appearance, pH, Osmotic pressure, obviously visible foreign matter, etc. are studied.

In terms of cell viability and proliferation ability, applicable detection methods can be used, such as Viable cell counting, cell doubling time analysis, cell cycle analysis, colony formation rate analysis, etc.

The production and/or use of certain immune cell therapy products may require the By mixing different types of cell products, the mixing characteristics of the products can be Quality studies and identification of critical quality attributes of blended products. Before mixing, it should be Carry out relevant quality research on each independent immune cell therapy product, respectively. Determine the respective critical quality attributes.

(2) Quality control

1. Quality Standard

Quality standards need to be based on comprehensive risk analysis, accumulated production and clinical research research experience and statistical analysis (if applicable), reliable scientific knowledge, combined with Formulated based on the results of quality studies, stability studies, etc. Quality standards include inspection items Objectives, testing methods and standard limits. Sample testing can be reasonably set up according to testing needs testing stages, such as intermediate samples, release testing, retained samples, etc., to effectively control product quality. Inspection items generally include identification, biological activity, purity, impurities quality, transgene copy number (if applicable), cell number (number of viable cells, function cell number/proportion, etc.) and general testing (such as pH, osmolarity, sterility, mycoplasma body, bacterial endotoxin, appearance, obviously visible foreign matter, etc.).

(1) Inspection items and testing methods

Cell identification: It is recommended to use appropriate and specific detection methods. When necessary, multiple methods are used for identification. The methods used may be cell morphology, HLA analysis, genetic polymorphism analysis, karyotyping, STR analysis, metabolic enzymes Subtype profiling analysis, cell surface markers and specific gene expression product analysis, etc.

Purity: Combined with quality research, select purity testing indicators based on product characteristics. Targets, such as cell surface markers, specific biological activities, etc.

Sterility and mycoplasma: According to the "Chinese Pharmacopoeia" sterility test method and mycoplasma Inspection method to detect bacteria, fungi and mycoplasma. When the test sample size is restrictions, or special circumstances such as rapid release, if pharmacopoeial methods cannot meet the requirements, Consider developing new sterility and mycoplasma detection methods for release testing. However, new detection methods should be fully validated. During the data accumulation phase, you can Well-validated novel methods and pharmacopoeial methods are used in parallel.

Bacterial endotoxin: According to the bacterial endotoxin test method in the "Chinese Pharmacopoeia"

Detection of bacterial endotoxins or other suitable validated methods.

Endogenous and exogenous viral factors in cells: Determination of immunity based on results of quality studies

Immune cell therapy products and endogenous and exogenous viral agents that may be introduced during their production

On this basis, select appropriate methods such as cell culture, nucleic acid or protein

Detection methods, fluorescent antibody detection methods, etc. are used to detect endogenous and exogenous viral factors.

Replicating viruses (RCV): For genetic modification using viral vectors

For immune cell products, RCV is an important safety risk concern, in addition to

In addition to the detection and control at the viral vector stage, the final cell product also needs to establish a complete detection and control system.

testing and risk control strategies. When cell release testing uses a rapid RCV detection method

When testing, it is recommended to retain samples. Used during clinical trials or in the early stages of marketing

It shows that the cell culture method uses reserved samples for parallel detection and analysis to accumulate data; in the above

In the post-market maturity stage, retained samples can be used for research and analysis when necessary.

Biological activity: It is recommended to select a product that can characterize the biological activity of the product and is suitable for use.

Methods for release testing. In some cases, such as products with multiple mechanisms of action,

Or when a single detection method cannot fully reflect its mechanism of action, it may be considered

Use more than one method for biological activity detection.

Impurity control: According to the results of production process and quality research, clarify the product

Process-related impurities and products that remain during the production process and may affect product quality

For product-related impurities, select appropriate methods for detection and control. For general workers

process-related impurities, if it is fully verified that the process can effectively and stably remove them

In addition, it can be controlled in conjunction with the process.

Tumorogenicity/Tumorigenicity: If applicable, may be considered based on quality study results

Whether to include tumorigenicity/tumorigenicity control items.

In addition to the testing items and methods listed above, it can be combined with actual research conditions

Make reasonable adjustments to the situation.

(2) Standard limits

Quality standard limits can be established based on product development-related data, non-clinical research

Research batch testing data, clinical trial batch testing data, process verification data and

and stability research data, etc., while taking into account the characteristics of the product and the current scientific

Cognition and consensus. It is recommended to focus on formulating standards based on the testing data of clinical trial batches.

accurate limit.

2. Validation of detection methods

Detection methods should be researched and verified, especially self-developed product specificity

Methods. Methods included in the pharmacopoeia should be confirmed for applicability. Pharmacopoeia Methods

When revised or replaced, its rationality needs to be verified.

Methodological validation studies need to pay attention to positive controls, negative controls, inhibitory controls

Photographs (if applicable), representativeness and sampling volume of test samples, testing indicators, judgment

The rationality of setting standards and other aspects.

For products with short shelf life or small sample size, rapid, micro-

A new quantitative detection method. New detection methods should be fully validated and

Compendial test methods are compared and evaluated (if applicable).

If there is a change in the detection method during the research and development process, the changed method should be

Evaluation and research to demonstrate that the proposed change method is superior to or equivalent to the pre-change method.

3ÿ Standard/Control

If conditions permit, standards/controls can be established as needed.

To meet testing needs and help ensure equipment and reagents are within specified ranges

Work within the system to improve the reliability and accuracy of test results.

The standards/controls established must have a clear intended use and use validated

Test and calibrate detection methods, and develop standards/calibrators used at each stage

The source of the reference product should be traceable, and corresponding stability studies should be conducted.

4. Other cases

Product release testing is an important guarantee to ensure that product quality meets clinical application

barriers, but some immune cell therapy products may not be available clinically due to their short duration.

Complete all release testing before bed use. In this case, if the risk is charged

If it is evaluated through separate research and verified and proven to be controllable, it can be considered to complete the

The entire release is used before the test results are obtained (use release); when the risk has not been

Sufficient research and assessment or assessment that it may cause serious irreparable consequences

, it is not recommended to consider using release.

In order to strengthen quality control and reduce risks, it is recommended to consider the following measures:

(1) When release testing time is limited, consider improving the quality of raw materials

Control and process controls, combined with release testing, to control risks.

(2) In terms of detection methods, rapid alternative detection methods can be used for detection.

To control risks to the greatest extent. Before validation of alternative test methods can be fully completed, it is necessary to

Carry out parallel testing of pharmacopoeia methods and alternative testing methods, accumulate data and conduct research

Continuously optimize during research.

(3) While using release, complete release testing should continue to be completed.

It is necessary to fully consider the relevant risks and formulate measures in advance. When the subsequent release testing is completed,

If an abnormality or non-conformity occurs, an emergency plan applicable to the relevant risks must be activated.

5ÿ Quality approval before use

Products require quality approval before administration, especially in the presence of pre-use cells

Recovery, dilution and other operations. Approved content may include, but is not limited to: Standard

Signing and verification; storage and transportation conditions review; operating steps review; appearance, obviousness

Observation of visible foreign matter; observation of cell morphology (if applicable); number and proportion of viable cells

Determination (if applicable); rapid sterility test (if applicable), etc.

8. Stability research

The stability study of immune cell therapy products is obtained through designed experiments.

Its quality attributes vary under the influence of various environmental factors (such as temperature, freezing and thawing, etc.)

The law of time change is the product quality standard and product expiration date (or intermediate sample

An important basis for formulating the temporary shelf life of the product. At the same time, it can also be used to determine process parameters,

Whether the preparation prescription, packaging materials, etc. are reasonable.

(1) Basic principles and storage stability research

Immune cell therapy products can refer to the stability research of general biological products.

requirements, and based on the characteristics of the product itself, the needs of clinical medication, as well as packaging,

Design a reasonable study plan for storage and transportation situations.

Samples for research: According to the needs of the specific production process and the availability of the corresponding cells

availability, select representative samples for research, including starting cells collected,

Intermediate samples during the production process, finished cell products, samples during clinical use, etc., research

Production, use and quality of research samples (such as total cell density and volume range, etc.)

Should be representative of actual conditions. Sample packaging containers and sealing systems should be selected and practical

Small-sized packaging containers and sealing systems of the same or the same material for actual storage. For self

In vivo immune cell therapy products, if the patient's use of cells is limited, you can use

Conduct studies using representative healthy donor cells.

Inspection conditions: Based on the actual conditions of the product during storage, transportation and use

Select reasonable and comprehensive stability investigation conditions based on the situation and possible exposure conditions.

For example, for finished cells, starting cells or intermediate samples that need to be frozen and stored,

It is necessary to study the cell quality (such as cell number, viability,

(appearance integrity, function, etc.); if necessary, it can also be studied multiple times

Effects of freezing and thawing. In addition, the product may be stored, transported, and used according to the possible

Exposed to severe conditions, conduct research on influencing factors such as high temperature, irradiation, and vibration.

Testing indicators and testing methods: usually combined with product characteristics, set reasonably,

Comprehensive testing indicators, including but not limited to physical and chemical properties, cell viability, purpose

Cell proportion, biological activity, microbial safety indicators, etc. Research needs to be reasonable

Set the inspection frequency of each indicator, such as at least at the beginning and end of the proposed validity period.

Perform sterility tests or alternative tests (e.g. container/closure system integrity test) at regular intervals

test). If the stability data indicate that the excipient may oxidize or degrade during its validity period,

When the solution, etc. has an adverse effect on product quality, it is necessary to conduct

Excipient content or related activity should be monitored. The detection methods used should be validated

Research can sensitively reflect the changing trend of product stability.

(2) Research on transportation stability

Immune cell therapy products usually require cold chain transportation, and the transportation process of the products The process should conduct corresponding stability simulation verification studies. Stability studies need to fully consider Consider transportation routes, means of transportation, distance, season, time, conditions (such as temperature, radiation, vibration, etc.), product packaging (such as outer packaging, inner packaging, etc.), Product placement and monitor status (such as the number and location of temperature monitors, etc.) and other factors, it is recommended to conduct research by simulating the worst conditions of actual transportation. right For finished cells, starting cells or intermediate samples stored in suspension in liquid, it is necessary to In your research, pay attention to the orientation of the product (e.g., upright, inverted, or horizontal). etc.) and the effects of oscillation on cells. Confirm the product through transportation stability studies The stability of the product can be maintained under the proposed storage conditions during transportation. Build concurrently It is recommended to evaluate the impact of a product temporarily out of the intended storage conditions (e.g. when the product leaves the cold chain). temperature, times, total time, etc.) on product quality.

(3) Study on stability of use

When using stability study designs, actual clinical use scenarios should be considered. Impact of product quality, such as syringe and needle types, aspiration versus bolus and drip rate, type of intravenous infusion tube, infusion pressure, and administration ring Environmental conditions (such as temperature, light, etc.) and time, etc. For needs during use For samples to be recovered, diluted, mixed and/or staged, studies are required to support production The stability of the product during use and storage. In the stability study of use, it is also necessary to pay attention to the operation Risk of microbial contamination introduced during operation. Based on usage stability study data Reasonably formulate the storage conditions and time after thawing or clinical compatibility of the product.

(4) Storage condition labeling

According to the stability study results, it needs to be clearly stated in the product instructions and/or labels

Product storage conditions and expiry date. Products that cannot be frozen need to be stated separately. like

Products require radiation protection or freezing and thawing, etc. It is recommended to put labels on various types of container packaging

and noted in the instructions.

9. Packaging and sealed container systems

Materials, storage containers and packaging materials to avoid contact with samples during production

Materials have an unintended impact on the quality of immune cell therapy products and require safety measures.

Safety assessment, compatibility studies and functional suitability studies.

In terms of safety assessment, the material components, their sources, and the production process need to be

Risks that may be introduced by the process (if applicable) and quality control to ensure adequate safety

sexual assessment. Basic performance testing and production of packaging materials by suppliers can be used

The results of the physical safety assessment shall be used as a reference basis.

In terms of compatibility research, the basic principles can be referred to general biological product packaging materials.

Compatibility study requirements. Based on risk assessment, direct contact materials or

Containers undergo extractables/leachables studies and undergo safety assessments. researching

Ingredients with higher compatibility risk (such as excipient DMSO) and materials need to be fully evaluated

Or the interaction of containers, etc.

In terms of functional applicability, container tightness/tightness, freezing

Research on applicability, etc.

In addition, for secondary packaging containers for transportation (not in direct contact with cells)

Verification studies should also be conducted on materials or materials, including but not limited to thermal insulation,

Aspects include sealing, resistance to mechanical pressure and light-shielding (if required).

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