Current Considerations on Chemistry, Manufacturing and Control of Cell Therapy Products (CTPs)

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Cell therapy has emerged as a promising new treatment in medicine.

Challenges remain in ensuring consistent quality, clinical efficacy and safety profiles.

- Diversity of cell types
- Complex manufacturing process
- Clinical indications
- Limited regulatory experience
- Cell therapy products characteristic (heterogeneity, \textit{ex vivo} manipulations, \textit{in vivo} renewable, persistence and expansion, the immune response etc.)

Scientific consensus and regulatory measurements are urgently needed.
Background

- In China, CTPs are joint regulated by National Medical Products Administration, **NMPA** (previously known as China Food and Drug Administration, **CFDA**) and National Health Commission of the People’s Republic of China, **NHC** (previously known as National Health and Family Planning Commission, **NHFPC**)

- Laws, regulations and guidance

*Drug Administration Law*

*Clinical Trial Provisions for Stem Cell-based Medicinal Products, 2013*

*Guideline on Quality Control and Pre-clinical Study of Stem Cell-based Medicinal Products, 2013*

*Guidance for Research and Evaluation of Cellular Therapy Products, 2017*

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Background

- More 100 CTPs communication meetings has been held.
- 26 CAR-T products have been filed for IND (investigational new drug) to CDE,NMPA by 2018/9
- 5 CAR-T products have already been approved for clinical trial
- Stem cells: less than CAR-T products, but the number is increasing. One stem cell product is under pre-NDA communication meeting.
Outline

• Raw materials and excipients
• Process development and control
• Quality study and control
• Products stability and shipment
Raw materials refer to original cells, ancillary materials and devices or components in the combined products.

Raw materials and excipients used in CTP preparations may potentially affect the safety and quality of final products, and should be carefully selected, well defined and thoroughly evaluated.

The quality and/or grade should be suitable for the intended use. Pharmaceutical grade or regulatory authorized materials are recommended.

Provide a list of all RM and excipients and risk analysis (source, quality, safety data).
Raw materials and excipients

◆ Safety

✓ transmitting pathogenic viruses → avoided
✓ residue of impurities → limited
✓ high risk materials → justified when use
✓ chemically defined medium without serum and serum-free cryopreservation medium → encouraged
✓ quality requirement → approved products
✓ toxicity study and assessment in animal models may be necessary (in some cases)
✓ donor eligibility → thoroughly assessed and defined

◆ Consistency

✓ Medium
✓ Vectors (purity, titer)
✓ Original cells (in process control is recommended)
Raw materials and excipients

- Medium (cytokines) and Serum
- Producing cells
- Vectors
- Excipients
Raw materials and excipients

Medium (cytokines) and Serum

Medium (cytokines): selected for specific CTPs. support cell growth; suitable for stem cell differentiation.

Serum: necessity and rationality (amount)

- AB Serum
- Patient-shelf serum
- Bovine serum
Raw materials and excipients

Medium (cytokines) and Serum

- safety (adventitious virus) and consistency
- Regulatory perspective
  - Use chemically defined, risk-controlled medium
  - Do not use or use limited serum, replacement of serum
  - Inspect and audit the producers and/or suppliers
Raw materials and excipients

Producing cells

• Origin, history culture and/or genetic construction (clear and risk assessed)
• Characterization (identity, purity, genotyping, phenotyping and integrity of the introduced sequences) (clear and meet the requirements)
• Adventitious virus
• Bacterial and fungal contamination, mycoplasma and some other specific contamination (test and tight control)
• Banking system and comprehensive testing
Raw materials and excipients

Vectors (virus, Piggybac etc.)

- Proper design
- Risk analysis
- Producing system
  - Plasmids (banking, GMP)
  - Environment (GMP)
  - Purification (chromatography)
- Testing (purity, titer, RCL/RCR)
- Storing

Suggest defining vectors as raw materials
Production process and testing are required
Quality Requirements = gene therapy products
Raw materials and excipients

Excipients

✓ Pharmaceutical grade or regulatory authorized materials are recommended
✓ sterility and endotoxin-limited
✓ interactions with cells
✓ interactions with package
✓ category, amount and administration route (reference)
Process development and control

- Identifying and refining manufacturing system
- Manufacturing environment
- Robust process and changes
Identifying and refining manufacturing system

- Isolation of original donor cells and ending with administration of processed cells into patients.
- The manufacturing process mainly consists of cell isolation, cell characterization, cell induction or gene modification, cell culture or amplification, purification, testing, storage and delivery.
- Development of manufacturing process: design, adjusting, confirmation, validation and finalization.
Identifying and refining manufacturing system

- Taken into consideration: scalability, automation, intermediate product stability, sterilization operation, process control and general process robustness/failure rate and supply chain.
- Reliable, robust and economical process.
Critical parameters in the process should be determined and defined.

- Temperature, pH, and dissolved oxygen → key parameters → cell growth kinetics, cell age and cytokines secreted
- Agitation → phenotype of shear-sensitive cells
- Dissolved oxygen → potency and purity of pluripotent stem cell (PSCs), HSPCs and MSCs
- Level of oxygen and the concentration of fibroblast growth factor 2 (FGF2) → differentiation capacity and phenotype of MSCs.
- Accumulation of metabolic byproducts (lactate or ammonium, decreased pH) → inhibition of cell growth and the loss of PSC phenotype
- Medium exchange rate and different culture strategy (fed-batch or perfusion) → accumulation of waste products and factors secreted.
- Cooling rate of cryopreserved → cell survival rate.
- Vector purity and transduction ability → CAR +T ratios
• Good Manufacturing Process (GMP) is required for human use product producing.

• The viral or infected materials in the conditions involving the infected donors and replication competent vectors should be prevented to spread and be kept in tight control.

• Furthermore, adequate measures should be taken to ensure products traceability and avoid cross-contamination and mix-ups.

• The automation techniques, in-line sensor systems and strict management of aseptic will be expected to help improve quality control and minimize the run-to-run variability, especially for large-scale manufacturing of allogeneic therapies.
Process evaluation/validation

- Critical manufacturing parameters
- Appropriate monitoring and control measures
- Validation of aseptic manufacturing conditions
- Establishment of cell banks kept as seeds for repeated bathes to enable bath-to-bath consistency is recommended.
- Donor-to-donor variability in individual therapies and run-to-run variability in allogeneic therapies may be handled with proper investigation and control on the systematic manufacturing process to minimize the variability.
Process evaluation/validation

• Manufacturing parameter changes → product comparability study (safety, identity, purity or potency etc.)
• Comparability study should be based on risk mitigation strategy, and changes with high risks would require more data including clinical data to support the rationality of changes proposed.
• Site change for CTPs: limited experience
• In principle, It is required to file the changes and comparability study data to regulatory authorities before any actions are carried out or it is recommended to communicate with the regulatory authorities for comments and advise.
Quality study and control

- Comprehensive research and analysis of the quality profile of CTPs are required (generally include safety, potency, identity and purity etc).
- Usually conducted before and during clinical trials as well as when any changes which could potentially impact product quality may occur.
- The acceptance criteria of product release specification could be justified via quality study.
- The trend analysis is necessary at proper intervals. Moreover, the batches selected for quality study should be representative of those that would be used in clinical trial. (healthy donors vs patients)
Safety

• Contamination: microorganisms (bacterial, fungal and mycoplasma), endotoxin, cell cross-contamination, non-cell particulates (like plastic fragments, residual microcarriers and fibers) and ancillary materials residues.
• Cell malignant transformation, may present as beyond the limit of cell passage number
• Off-target toxicities (CAR-T)
• Tumorigenic and tumor growth promotion (virus vector)
• Recovery mutation of viral vectors (RCR, RCL)
Identity

◆ Identity of cell origin and function
◆ More than one cell identity tests for one single product
  Ø Combined MSCs have varying properties from different tissue sources.
  Ø CAR-T products is necessary to demonstrate chimeric antigen receptor and T-cell markers double-positive cells in order to discriminate against un-transduced T cells and undesirable cell types.
◆ Challenges and limited knowledge (MSC, CAR-B)
Potency

• Mechanism of action or effect
• Potency of MSC could be the assays describing the engraftment and tissue formation, or the secretion of paracrine factors etc.
• Potency of CAR-T cells would be measured as the ability to destroy the target cells and cytokine release, proliferation and/or degranulation
Strength

- For CTPs, strength could be cell sub-population, density, number and/or viability.
- Strength could be measured in different assays
- Demonstrate the most appropriate kind of assay
- Other factors, such as population composition, mitochondrial content or activity, substrate abundance may be properly taken into consideration.
Purity

• Impurities → undesirable cells, contamination, ancillary materials residues and particulates etc.
• Impurities may cause compromised effects and immune complications
• Impurity thresholds should be set up and confirmed by testing results from animals and/or humans and from experience.
• Thresholds for purity may vary according to the products.
Quality control

Final Product

IPC

Raw materials

Intermediate product

Packaging materials
Specification

• Quantity, identity, purity and biological activity etc.
• Set limits for impurities (safety)
• Tests cannot be performed on DS or DP, only on key intermediates and/or as in-process tests ➔ justified
• Product quality check (hospital)
Testing Methods

• Based on the best available science
• Robustness, reliability and capability should be validated
• Provide results before release for clinical use or alternative methods are applied (justified and emergency measurements)
Products stability and shipment

- Liquid suspensions → fresh shipment
- Cryopreserved products → phase transition, osmotic intolerance, cryoprotectants and warming/thawing temperature could cause cell injury
- Type and concentration of cryoprotectants (DMSO)
Storage container

- Directly contact with product
- Functional evaluation (the capacity to withstand the outside temperatures, fulfill the light-sealed and liquid-sealed requirement, etc.)
- Feasibility (product characteristics, storage condition, handling and shipping conditions as well as maintenance of suppliers etc.)
- Compatible (with the freezing solvent)
- Label (well designed, easy to identify, compatible with transport and storage conditions as well as avoiding mix-up)
Shipment

- Shipment will impact the product quality as the end of the chain.
- Validate the shipment process, including temperature, humidity, transportation, route, secondary packaging, duration and monitoring system.
Challenges

• Still a lot need to be explored about how to characterize these “living” drug products before administration
• More needs to be understood about how different manufacturing strategies can affect safety and efficacy
• Considering the varieties and complex of CTPs, the principles of manufacturing control and quality control from the perspectives of scientific and regulatory considerations should be made and followed.
• With improved medical practice, more abundant experience, better understood mechanisms and optimized protocols, the risks may be reduced and better controlled.
Thank you for your attention!

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