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SPECIAL REPORT

Guidelines for Packaging, Transport, and Storage of Source Cells for Organoids

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This report presents guidelines for the systematic management of packaging, storage, transportation, and traceability of source cells used for organoid research. Given the important role of source cells in organoid studies, it is important to ensure the preservation of their quality and integrity throughout transportation and distribution processes. The proposed guidelines, therefore, call for a cohesive strategy through these stages to minimize the risks of contamination, deterioration, and loss–threats that significantly compromise the safety, efficacy, and efficiency of source cells. Central to these guidelines is the quality control measures that include roles and responsibilities across the entire supply chain, with recommendations specific to packaging materials, transportation facilities, and storage management. Furthermore, the need for an integrated management system is emphasized, spanning from source cell collection to the final application. This system is crucial for maintaining the traceability and accountability of source cells, facilitating the sharing, distribution, and utilization on a global scale, and supporting to advance organoid research and development.

Keywords: Organoids, Guideline, Stem cells, Packaging, Transportation

Introduction

To produce high-quality organoids mandates the implementation of stringent quality control protocols (1) across their lifecycle, encompassing production, dissemination, and preservation phases. This involves a spectrum of quality assessments for source cells, extending from the point of manufacture to their final packaging, storage, transport, and eventual application. Key factors in this process are the assurance of optimal environmental conditions (2), including temperature regulation, protection against physical damage, and verification procedures for transport systems. The substantial financial and logistical challenges inherent in the production and transportation of source cells accentuate the need for thorough management to prevent loss through negligence, thus raising concerns pertaining to safety and efficacy in manufacturing, packaging, transportation, storage, and manipulation of

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source cells. The growing application of organoids in medical research (3-6) worldwide is attributed to their potential in recapitulating bodily functions. In this context, standardization of source cells (7) is viewed as a crucial step toward enhancing the quality and uniformity of organoid products (8) and their widespread dissemination. The deployment of objective evaluation mechanisms for source cells, coupled with the implementation of product traceability systems, are seen as strategic measures to sustain and validate product quality and homogeneity. Standardized coding and labeling of source cells, in conjunction with uniform procedures ranging from cell collection to final use, seeks to advocate a systematic framework for efficient cell management. The guidelines describe the essential considerations and risk management for packaging suppliers, source cell providers, transportation service providers, and end-users. The overarching aim is to ensure the quality, safety, and efficacy of source cells throughout their distribution process, emphasizing the critical nature of adhering to quality control measures to mitigate risks in the lifecycle of organoid production and use.

Management of Packaging for Source Cells

Source cells require precautions against contamination by external substances under different environmental or thermal conditions. Selecting appropriate packaging methods and materials requires an evaluation of the cells' physicochemical, biological, and microbiological properties. Moreover, to prevent alteration, contamination, deterioration, or damage to the cells during storage, transportation, and handling, and to maintain quality control, it is necessary to assess and ensure the suitability of chosen packaging solutions against established criteria (9).

Roles and responsibilities in packaging operations

Supplier:

a. The supplier is required to provide emergency contact information on the packaging materials to support a prompt response to any emergent issues.
b. The supplier is required to provide the packaging material supplier with detailed information on factors that could interact with the source cells, including cell preservation solutions and culture media as well as other factors that may compromise cell quality.
c. When custom packaging is required, the supplier should clearly communicate the specifications for the packaging materials to the packaging material supplier and request custom packaging solutions.

Packaging material supplier:

a. The packaging material supplier should evaluate the information provided by the supplier regarding factors affecting quality and the potential interactions with the contents. Subsequent to this evaluation, it is important to engage in discussions with the supplier to determine the necessity for additional information.
b. Following the specifications provided by the supplier, the packaging material supplier is tasked with provision of packaging solutions that provide adequate protection and maintain the stability of the contents within.
c. The packaging material supplier is responsible for producing packaging materials that meet the supplier's specified requirements. If standard packaging materials do not satisfy these requirements, the supplier should develop custom packaging solutions tailored to the specific needs.
d. The responsibility of the packaging material supplier extends to sourcing sustainable packaging materials. This involves the use of mono-materials to enhance recyclability where possible and designing of packaging solutions that can be produced through environmentally friendly processes.

Management of packaging materials

Packaging materials can be categorized into primary packaging materials, which are in direct contact with the product, and secondary packaging materials, offering additional protection without directly contact. The design of primary packaging may include an inlet for functionality.

Primary packaging materials:

a. Direct-contact materials, such as containers, inlets, and stoppers, should be evaluated for compatibility, structural integrity, and their impact on cell viability through stability tests to ensure long-term preservation (10).
b. The primary packaging should protect the product from quality-degrading factors including:
   1) Temperature: ultra-low temperatures below −150℃, low temperatures below −60℃, temperature fluctuations during freezing and thawing, and uneven temperature distribution
   2) Light
   3) Reactive gases: oxygen and carbon dioxide
   4) Contaminants: microorganisms (bacteria, fungi, viruses), particulates, and external substances
   5) Physical forces: deformation, vibration, and shear stress
   6) Moisture absorption
   7) Leakage: loss of cell preservation solution
c. Interactions between packaging components and contents–such as extractable/leachable, pH changes, endo-

toxins, cytotoxicity, mycoplasma, gas permeability–should not alter the cells or preservation solutions. Other such interactions include:

1) Absorption of source cells and cell preservation solutions by packaging components
2) Decrease in cell preservation solutions due to absorption or dissolution of absorbed substances
3) Sterility or aseptic barrier properties

d. Packaging components, including adhesives and inks, should be free from harmful substances. This is assessed through extraction and toxicity testing of packaging components, providing evidence for packaging material stability.

Secondary packaging materials: Secondary packaging materials, distinct from primary packaging materials, do not contact the product directly but provide additional protection. The functions include preventing movement of contents or gases, shielding from physical damage, and maintaining microbiological sterility.

Inlet: In packaging containing source cells, inlets serve multiple purposes: content injection, preventing leakage, providing a sterile connection pathway, maintaining pressure via filtration vents, allowing for addition of dilution solution for cleanliness.

Management of packing operations

The packaging of source cells should align with manufacturing workflows and adopt procedures tailored to characteristics of the source cells.

a. Because the source cells are living organisms, sterilization or filtration is not feasible; thus necessitating aseptic packaging methods similar to manufacturing processes.
b. Direct-contact packaging materials should be pre-cooled to match the source cells' temperature to ensure quality control.
c. Validation of the quality assurance period is necessary due to potential cell death, reduced cell activity, and cell aggregation, which can affect shelf life.
d. Cryopreservation methods should be validated to prevent alteration in source cells' fundamental characteristics during freeze-thaw cycles.
e. For autologous source cells with small batch sizes, applying sterility, virus, mycoplasma, and potency tests is challenging (11).
f. Packaging should include detailed source, temperature, condition, and identification information of the source cells, using labels, barcodes, or chips, ensuring:
-Label information should not be easily erased.
-Labels should securely adhere to the packaging material across storage conditions.
-Labels should retain adhesive properties even under extreme conditions such as freezing.
-Compliance with regulatory standards is required.
-Barcodes are preferred for their accuracy and information capacity.

Risk assessment and control during packaging

Identifying and mitigating risk factors is important during the packaging of source cells.

Risk assessment during packaging: Key risks in packaging source cells include: Deformation or alteration of cells, cross-contamination risks, variability in packaging materials, human errors in packaging process, differentiation between compatible and incompatible materials.

Risk management during packaging:

a. Test packaging materials to ensure they do not compromise cell integrity or contain harmful substances.
b. Implement segregation strategies in simultaneous or sequential product packaging to prevent cross-contamination and confusion.
c. Prior to packaging, check for any residual material from prior operations and align product quantities with packaging resources, correcting discrepancies, and managing leftovers accordingly.
d. Record packaging quantities and personnel details for risk traceability.
e. Store packaged products separately until quality approval is obtained (12).

Management of Source Cell Transportation

Transportation management of source cells covers from supplier handover to delivery, emphasizing the preservation of their physical, chemical, biological, and microbiological properties. Ensuring transportation conditions, traceability, and effective communication between suppliers and carriers all impacts cell quality, stability, and efficacy. Therefore, establishing transportation standards for planning, execution, tracking, and documentation is essential (13).

Roles and responsibilities in transportation operations

To ensure seamless transportation of source cells, operations should be divided into designated responsibilities. Each stage requires assigned personnel to manage quality through specification adherence, documentation, and record-keeping.

Supplier:

a. Certify and convey source cell information and conditions to the carrier and customer via shipping certificates.

b. Determine optimal transportation, storage, and handling conditions, based on cell stability and transportation test outcomes.
c. Provide carriers with information about the source cells to be transported to the carrier.
d. Ensure that source cells identifiable with barcodes and labels compliant with Global Standards 1 standards.

Carrier:

a. Safely transport source cells to the customer, maintaining quality within a specified period.
b. Implement transportation specifications received from the supplier, ensuring planning and execution align with source cell requirements.
c. Communicate transportation progress and status in real-time with supplier and customer, maintaining records at each stage of transportation.

Customer: The customer should facilitate information exchange regarding the destination and contact details for secure source cell transfer.

Management of transportation facilities

Transportation facilities:

a. Assign responsible personnel for transportation operations.
b. Ensure efficient inflow and outflow of source cells, error prevention, and stage-wise documentation.
c. Implement measures against contamination, theft, or loss during transit.
d. Maintain detailed records of transportation conditions and inspections to monitor source cell status.
e. Regularly clean and inspect transportation means for operational integrity.
f. Outsource transportation equipment validation if necessary.
g. Use Transportation containers and vehicles that ensure source cell integrity and safety during transportation.
h. Maintain appropriate temperature control for temperature-sensitive cells.

Transportation containers:

a. Transport involves primary packaging containers for direct cell contact, secondary protective packaging, possibly external containers with cushioning for condition maintenance and damage protection. Impact of cushioning materials should be pre-verified.
b. Use auxiliary containers with cushioning and absorbents for fluid containment in case of leakage, adjusting absorbents based on container temperature.
c. Arrange source cells to avoid mix-ups during transport.
d. Ensure transportation containers are suitable and made from materials resistant to leakage, shock, pressure changes. Include handling instructions to avoid potential damage such X-ray exposure prohibitions.
e. Special transportation containers must be regularly inspected and maintained to ensure functionality.
f. Keep detailed records on the performance, materials, cleaning, and maintenance of reusable containers and accessories.

Transportation vehicles:

a. Contractual agreements should explicitly outline situations requiring the opening of delivery containers or vehicles, with unauthorized access strictly controlled.
b. Regular validation of cooling/freezing performance is essential for refrigerated or frozen transport, accounting for travel distance, duration, seasonal changes, and product specifics.
c. For temperature-controlled transport, documentation affirming product specifications and temperature control verification must be pre-reviewed by customers or providers. Containers may include advanced temperature control features such as cooling/heating materials, automatic temperature control systems, and dry shippers with liquid nitrogen.

Automatic temperature loggers: Automatic temperature loggers should record container temperature to ensure maintenance within acceptable ranges during transportation, activating alarms if preset limited are exceeded. Transportation service providers should set appropriate temperature limits, based on the permissible temperature ranges during transportation and the qualified ranges of temperature-controlled containers. The loggers should be regularly calibrated. Records from the loggers should be periodically reviewed to confirm transportation conditions.

Management of transportation operations

Carriers are tasked with delivering source cells as per supplier specifications within designated timelines.

Preparation for transporting source cells: Suppliers should issue shipping certificates, detailing source cell conditions and specifications, for carrier and customer. This certificate should accompany the product through all transportation stages to define responsibility boundaries.

Checkpoints for transporting source cells: Carriers should match shipping certificates with actual products, using barcodes and labels at the site of product receipt, ensuring transportation methods align with specified conditions. Products should be transported separately to prevent product mix-ups, with comprehensive records maintained for each transportation phase, including receipt timestamps, signatures, and inspection results. Customers should verify received source cells against shipping and transportation records.

Risk assessment and control during transportation

Identifying and managing risk factors is important for maintaining source cell quality during transit.

Risk assessment for transportation: Risk assessment should consider quality impact, occurrence probability, and potential consequences, focusing on temperature control deviations, transportation malfunctions, container damage, delays, natural disasters, contamination, and misdelivery.

Risk control during transportation: Carriers should develop transportation specifications to mitigate risks, maintaining communication with suppliers and customers regarding any encountered risks. Alternative transportation methods and routes should be prepared. Carriers should have temperature devices regularly inspected and calibrated by accredited institutions. All deviations and changes during transport should be documented and shared with involved parties.

Storage Management of Source Cells

Scope of storage operations

This section covers the management and inspection requirements for storing source cells under various scenarios, including post-packaging & pre-carrier receipt, temporary storage during transit, and customer storage post-receipt and inspection.

Storage operation management

a. Storage facilities should meet source cell storage condition requirements.
b. Unauthorized access should be restricted to safeguard against alterations, loss, or theft.
c. Facilities should employ locking mechanisms for theft prevention.
d. Visitor logs should record the details and purpose of any facility visits.
e. Regular checks and management of source cell inventory by designated staff are necessary.

Storage facilities

Storage facility management:

a. Transportation providers manage facilities for source cell storage and handling throughout transit.
b. Facilities should maintain appropriate temperature and humidity levels to prevent product degradation, ranging from ultra-low temperatures (below −150℃) to room temperature (+15℃ to +25℃).
c. Fire prevention, emergency power systems, and pest control measures are essential.
d. Facilities should have adequate lighting, ventilation, and shading for effective storage management.
e. Incident response protocols should be established.

Storage facility requirements:

a. Facilities should be conducive to proper cell distribution and preservation.
b. Sufficient storage space and area should be available.
c. Protocols in caser of equipment malfunctions or breakdowns should be in place.

Verification of temperature loggers:

a. Temperature loggers in facilities require regular verification and calibration.
b. Calibration records should detail calibration cycles, standards, and methods.
c. Accredited bodies should perform verification, with their certificates recognized for a set period.

Environmental management:

a. Documentation should outline cross-contamination prevention measures, including cleaning frequency and methods.
b. While pest control may be outsourced, the facility manager is responsible for environmental hygiene, entailing regular on-site reviews and verifications.

Document Management

Retention period

Documents crucial for traceability should be stored as per regulations defined by the Public Records Management Act (Presidential Decree No. 22575, Article 261(1)) and the Act on Safety and Management of Human Tissues and others (Law No. 18447, Article 20). These acts dictate retention periods ranging from 1 year to permanent preservation, based on specific criteria.

Types of documents

a. Shipping certificates: essential for verifying source cell quality among stakeholders.
b. Inbound inspection reports: validate the quality of received source cells against shipping data.
c. Performance records: include temperature, transportation, and calibration records for quality assurance and traceability.
d. Procedure documents: cover work instructions, product and transportation specifications, and contracts, all of which should documented and preserved.

Management system

Documents should be easily identifiable, searchable, and understandable, serving, for example, as training materials to ensure task and procedure clarity. The system

should allow relevant personnel access, maintaining up-to-date work and inspection procedures.

Risk management

Document systems should safeguard against unauthorized alterations or losses. Regular reviews ensure compliance with evolving legal, technological, and procedural standards.

Traceability Management

Definition of traceability management

Traceability management tracks source cell data from collection to productization and vice versa, addressing quality and stability issues promptly and effectively, with specific definitions varying by region.

a. European Union: EU Directive 2006/86/EC defines traceability as the capacity to track cells and tissues from collection to disposal, including identification of all relevant data such as donor information, and involvement of any entity in the handling process (14).
b. United States: according to HCT/P regulations (21 CFR Part 1271), traceability refers to the capability of institutions to monitor cells and tissues and their derivatives, ensuring the detection of infectious disease transmission and facilitating timely corrective actions (15).

Need for traceability management

With the growing distribution and use of source cells globally, traceability is important for managing the risk of disease transmission and ensuring rapid response to quality or stability concerns.

Measures for traceability management

A comprehensive traceability system should cover all aspects, from system configuration to codes and labeling and reporting anomalies. It should include detailed source cell information (such as collecting institution, unique ID number, types of source cells) and product information (such as manufacturer, product condition, disposal date), employing simplified, unified coding for efficient tracking.

Standardization needs for traceability

The international expansion of the source cell industry underlines the need for standardized information systems to facilitate global research cooperation. Standardization efforts should address the collection, management, distribution, and documentation stages to align with international norms. Areas of standardization include: (a) collection protocols for source cells, (b) consent documentation, (c) storage, management, evaluation, distribution, and sales processes, (d) documentation and analysis of source cell data, (e) Classification, quantity, and chronological data of source cells, and (f) Logistics and tracking mechanisms.

Standardization measures for traceability

a. Establish a supervisory organization with capable systems and personnel.
b. Develop standardized protocols for collection, storage, management, and use of source cells.
c. Implement a comprehensive tracing system for source cells and tissues, enhancing product quality and enabling global distribution.
d. Introduce a continuous information surveillance and tracing system to manage the entire lifecycle of source cells, prompting international collaboration and quality certification.

Conclusion

The guidelines presented provide a framework that promises to impact the field of organoid research. By addressing the critical aspects of source cell packaging, transport, and storage, the scientific community is equipped to ensure the integrity, viability, and reproducibility of organoids. As the field of organoid research continues to evolve, these guidelines will undoubtedly play a role in guiding researchers towards achieving discoveries and applications that have the potential to revolutionize biomedical research and therapeutics using organoids. Future efforts should focus on the continuous refinement of these guidelines in alignment with technological progress and emerging research needs, fostering a collaborative and standardized approach to organoid research globally.

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Potential Conflict of Interest

There is no potential conflict of interest to declare.

Authors' Contribution

Conceptualization: SJA, SJ. Data curation: DK, HBL. Formal analysis: DK, HBL. Funding acquisition: SJA. Investigation: DK. HBL, SL. Project administration: IUO, TSK, JHL. Supervision: IUO, TSK, JHL. Validation: IUO, TSK, JHL. Visualization: DK, CP. Writing – original draft: SL, SJA. Writing – review and editing: SL, SJA.

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