Quality and Safety in Transplantation and Advanced Therapies: Validation, Validation and Risk Control in an Accredited Tissue Institute

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ABSTRACT

With the evolution of cellular therapies and personalised medicine, tissue institutes are being called upon to play an increasingly central role in the management of...

Introduction

With the evolution of cell therapies and personalised medicine, tissue establishments are called to play an increasingly central role in the management of biological material for both autologous and allogeneic haematopoietic stem cell (HSC) transplantation and the production of advanced therapy medicinal products (ATMPs), such as CAR-Ts. The safe execution of these activities requires the implementation of complex quality systems capable of ensuring traceability, reproducibility and regulatory compliance.
In this context, the concepts of validation, validation, risk assessment and change control represent fundamental pillars, as outlined both by the international JACIE standards and by the State-Regions Agreement no. 49 of 25 March 2021, which introduced specific requirements for the collection and handling of HSCs in clinical and production contexts.

The Framework for Quality Systems for Clinical and Manufacturing Research.

The Italian Regulatory Framework: JACIE and State-Regions Agreement 49/2021

The JACIE (Joint Accreditation Committee ISCT-Europe & EBMT) standards, at their seventh edition in 2021, represent a reference point for quality in transplantation and cell therapy programmes. They include very stringent requirements on several aspects of handling activities, including change and risk management mechanisms.

These requirements are very strict.

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In parallel, the State-Regions Agreement no. 49/2021 strengthened the Italian regulatory framework, defining minimum requirements for tissue establishments operating as collection centres for starting material used in the production of CAR-T and other ATMPs. The agreement stipulates that processes must be validated and managed with formal quality systems, including change control, risk analysis and end-to-end traceability.

Validation and Validation: Operational Fundamentals

In a tissue establishment, validation is a systematic activity aimed at ensuring that the processes employed — from the collection of HSCs to their storage and distribution — are capable of producing compliant and repeatable results. There are three types of validation:

1. **Prospective**: carried out before the implementation of a process or equipment;
2. **Concomitant**: carried out during the first clinical productions under supervision;
3. **Retrospective**: applied using already available historical data (where justified);

&It is essential to examine individual processes within a tissue institute to define critical points for validation and validation.

In the case of starting material for CAR-T, validation involves:

- The evaluation of the collection conditions (temperatures, timing, sterile materials);
- The qualification of the personnel involved (according to JACIE and GMP);
- The control of transport and storage equipment;
- The verification of container integrity and labelling according to ISBT128;
- The evaluation of the indicators associated with the processes associated with the handling activity itself;

Analytical validation è therefore required for test methods such as cell count, post-thawing viability, bacterial contamination and endotoxin testing.

Risk Assessment: Prevent to Ensure

According to the State-Regions Agreement No. 49/2021, each process step must be subject to a formal risk analysis. The main purpose of this process is to identify critical control points (CCPs), to prevent adverse events linked to product non-compliance, and to guarantee operational continuity even in extraordinary situations.

Metodoductivity analysis.

Methodology

The most widely used technique is FMEA (Failure Mode and Effects Analysis), which involves:

- Analysis of each process step
- Assignment of scores to severity, probability and detectability;
- Risk Priority Number (RPN) calculation and corrective action planning;

A mathematical calculation is used to quantify a score associated with the detectability, severity and frequency of a given event, thus enabling the introduction of changes that bring about a calming of the risk calculated for a single event. The very change thus introduced must be part of a further evaluation system:

Change Control: The Management of Change

The **management of change (change control)** è another mandatory requirement to ensure the consistency and quality of processes. It applies each time a new item is introduced, such as a new supplier or reagent, a change in operating procedures (SOPs), the updating of management software or registration modules, the replacement or relocation of critical equipment and more generally any change that can be configured as having an impact on the continuation of the processing unit's business.

Each change is recorded in a **change log** and evaluated for its impact on both the quality and safety of the biological material, the validity of existing certifications and the need for re-validation or document revision. This approach enables the institute to prevent deviations and maintain compliance even in dynamic and expanding environments such as gene therapy.

Results and Advantages of the Integrated Approach

The combined implementation of validation, validation, risk assessment and change control has therefore led to an approach that is able to guarantee a reduction in document errors with a significant decrease in serious deviations during inspections notified by the National Transplant Centre. This has also led to an improvement in the efficiency of the collection and handling processes and specifically a better synergy with the CAR-T manufacturing centres, thanks to the standardisation of flows that have undergone variations based on requests from e.g. CROs.

Conclusions

Quality management in a modern tissue institute can no longer ignore a systemic approach that integrates validation, validation, risk assessment and change control. This model, in full adherence with the JACIE standards and the State-Regions Agreement 49/2021, guarantees not only patient safety, but also the reliability of the entire process vis-à-vis manufacturers and regulatory authorities.

In an era in which personalised medicine and advanced therapies are becoming more and more

widespread, it is essential that tissue institutes position themselves as strategic partners, capable of combining scientific innovation, regulatory rigour and a culture of quality.

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