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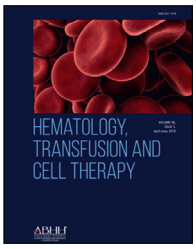

Special article

Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Consensus on genetically modified cells. VI: Accreditation process

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ABSTRACT

The adherence to accreditation programs proves the institutions' voluntary effort to pursue the quality and safety of their products and services by meeting internationally accepted standards audited by experts in the field, external to the service. Meeting such standards often exceeds domestic legal requirements. However, service providers are not released from complying with the legal requirements, both local and international, pertinent to the field. Accreditation programs use the precepts of the quality management system to validate and standardize processes, monitor results through quality control, proficiency testing, and indicators, and perform risk management. For cellular therapy services, the assessing agencies available in our field are the AABB/ABHH (American Association of Blood Banks/Brazilian Association of Hematology, Hemotherapy and Cellular Therapy) and FACT-JACIE (Foundation for the Accreditation of Cellular Therapy-Joint Accreditation Committee, ISCT/EBMT). Both agencies require that the accredited organization meets all the standards defined in each program. Applying services also have to establish and comply with a quality management standard that demonstrates procedural interrelationship to ensure product and service quality. This paper aims to concisely outline the essential features of those two accreditation programs, along with a brief overview of the accreditation process under each of them.

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Introduction

External audits represent the most effective means for institutions to have their processes evaluated. External audits can be mandatory or voluntary. Mandatory audits are carried out by regulatory authorities (e.g., the Sanitary Surveillance) and are termed inspections. Voluntary audits are performed by independent accrediting bodies whose specificity depends on the scope to be assessed. This chapter addresses non-mandatory audits (assessments), as a rule, offered by accreditation agencies. At present, domestic institutions seeking to obtain national and international accreditation have been striving to adapt to international quality standards, enabling them to become eligible to participate in the global flow of cell therapy products. Thus, submitting to audits of this nature offers institutions the best way to achieve the highest quality levels.

Hence, differentiating compliance with legal requirements regarding a specific area (mandatory) from accreditation requirements (voluntary) is crucial. By seeking accreditation, institutions aim to demonstrate their commitment to offering high-quality products and services, which in most cases exceed their country's legal requirements. The ISO 9000 series (International Organization for Standardization) defined the minimum and generic international standards for quality management systems applicable to all types of institutions and companies. Subsequently, institutional accreditation became applicable in several activity fields, including healthcare, despite its specificities.

For cellular therapy services, the assessing agencies available in our field are the AABB/ABHH (American Association of Blood Banks/Brazilian Association of Hematology, Hemotherapy and Cellular Therapy) and FACT-JACIE (Foundation for the Accreditation of Cellular Therapy-Joint Accreditation Committee, ISCT/EBMT). These accrediting agencies have adopted models that share several similar features. However, each accrediting agency has its inherent traits, as discussed further below. Both agencies require that the accredited organization meets all the standards defined in each program. Applying services also have to establish and comply with a quality management standard that demonstrates procedural interrelationship to ensure product and service quality. A distinctive feature in accreditation programs consists in the conduction of external evaluations by experts in the field. This differential provides greater accuracy - and therefore credibility - enables the exchange of experiences and fosters learning.

Accreditation models for cell therapy products in Brazil

AABB/ABHH accreditation

AABB/ABHH accreditation, which includes genetically modified cells such as CAR-T cells, involves complying with the standards issued by the AABB. These standards consist of ten minimum requirements, termed "Quality System Essentials" (QSE), and revised every 24 months. The fundamentals consist of ten chapters, which we will briefly discuss after discussing the general guidelines and the accreditation process.[1,2]

General guidelines (2)

The AABB/ABHH Standards for Cell Therapy Services have been developed following state-of-the-art and best medical practices. However, full compliance with them does not imply compliance with the pertinent national or regional laws, given that such laws may differ from the requirements outlined in the standards. In situations where Brazilian regulations are more restrictive than the standard indication, ABHH issues reinforcement bulletins to bolster the need to comply with the legal requirement.

The word "shall" in the standards indicates a mandatory requirement; its non-fulfillment characterizes non-conformity - except if the accredited institution had obtained a variance approval, previously requested to the accreditation body (or fully justified a posteriori). Conversely, the term "may" - scarcely used in the document- indicates a recommendation, thus not enforceability of the requirement to which it refers. The "pen" symbol, preceding a standard, designates the compulsory creation and subsequent maintenance of a log regarding the activity at stake. Log information derives from the control record tables included in the standard. The minimum retention period is ten years from development ("E" preceding the standard) or from the product's final disposition ("F" preceding the standard). In Brazil's case, legislation states that critical records must have a minimum retention period of 20 years, and non-critical registers must have a minimum retention period of five years. The strictest criterion must prevail.[3]

A glossary accompanies the AABB/ABHH Standards for Cellular Therapy Services to clarify the meaning of the terminology used in the Standards. Additionally, a "standards cross-reference" indicates the changes to each new edition of a Standard.[2]

AABB/ABHH accreditation process

The accreditation process for cell therapy products is step-based. The process starts with the “Application Form for Accreditation for Cell Therapy Services” submission to ABHH. The form undergoes analysis and may result in a contract for accreditation service provision. Next, the organization receives a copy of the Standards for Cellular Therapy Services to learn about the target requirements. The organization must then complete a Self-Assessment Checklist and submit it to the accrediting agency for analysis. Once all standards prove fulfilled, the external audit is performed.[4]

If any nonconformity arises during the external audit, the accrediting agency must register and report it to the accredited organization at the end of the assessment process. The organization must then analyze the root cause of the nonconformity, implement relevant corrective actions, and submit a formal written reply to the accreditation body. In case of the accredited organization's action plan approval, the applying institution receives a two-year accreditation certificate.[1]

The ten chapters mentioned above are briefly commented on and listed below.

Chapter 1 – organization

This chapter addresses the definition of the accredited organization's structure and quality management system, along with the technical and administrative requirements and responsibilities for each key role. The chapter also discusses the organization's commitment to meeting customer expectations and maintaining business continuity, even in risk situations, by developing contingency plans. A further issue addressed in this chapter concerns the accredited organization's assurance to comply with laws and regulations and any requirements imposed by the ethics committee on research involving human subjects (1.2).

Chapter 2 – resources

This chapter addresses the activities regarding the accredited organization's human resources management. The assessment includes the required qualifications to meet specific tasks. The professional qualification assessment examines the following items: educational background, training and experience, job description, roles and responsibilities of each position, training and continuing education programs, personnel identification and records, and competency assessments. Potential corrective actions in which the employee has participated are consideration issues (1.2)

Chapter 3 – equipment management

This chapter addresses activities related to the accredited institution's equipment management, including the characteristics of its facilities, their mode of operation, and performance. It also covers equipment monitoring, maintenance, calibration, and traceability issues. This chapter also covers the implementation, modification, and validation of the computer and database programs used by the organization. The chapter also covers the availability of alternative systems for ensuring access to critical information and continuity of operations in case of electronic data unavailability (1.2).

Chapter 4 – agreements and contracts

This chapter addresses agreements and contracts with third parties (national and international) and within the institution itself mandatory to carry out operations, including possible revisions and amendments. It also covers medical requisitions for product collection, processing, distribution, and informed consent forms for donors and patients. In addition, this chapter addresses issues concerning the relationship with overall suppliers and cell therapy services, including the need to submit them to evaluation, qualification, and monitoring, and eventually to notify them about any specific issue. It also defines the requirements for promotional and educational materials content offered by the institution (1.2).

Chapter 5 – process control (1.2)

This chapter addresses the definition of all activities involved in ensuring process predictability, stability, and consistent operation according to the criteria established by the institution's quality management system. Such control includes the following aspects:

- Defining and upholding adopted policies, processes, and procedures;
- Validating and monitoring critical processes through quality control, proficiency testing, indicators, outcome data, tracking, and trend assessment;
- Defining a structured change management process;
- Defining a materials management process (qualification, receipt, identification, handling, storage, use, and emergency use);
- Defining the processes regarding donor selection, collection, processing, distribution, release, cell therapy product administration and effect monitoring.

Chapter 6 – documents and records (1.2)

This chapter addresses the definition of activities related to identification, analysis, approval, alteration, conservation, and recovery of documents, as well as: creation, readability, alteration, confidentiality, archiving, and recovery of the institution's records. Additionally, it establishes that electronic records must be of controlled access, including guaranteed data integrity, as well as a safety mechanism for routinely keeping safety copies (backup).

Chapter 7 – product or service deviations and nonconformities and adverse events (1.2)

This chapter addresses the procedures for detection, documentation, investigation, impact assessment, correction, tracking, and notification of nonconforming events, including the recalls of nonconforming products in the event of their release.

Chapter 8 – internal and external audits (2)

This chapter addresses the activities to verify whether the organization's quality management system and operational activities comply with specified requirements. It focuses on undertaking internal and external audits, including clinical activities, including managing the audit outcomes.

Chapter 9 – process improvement (1.2)

This chapter addresses the requirements for determining the cause of deviations and actual or potential nonconformities. Next, the adoption of corrective and preventive actions, proportional to the magnitude of the detected problems, is

observed. Finally, it evaluates the effectiveness of such actions using the information gathered through the quality system toward operational improvement.

Chapter 10 – safety and facilities (1.2)

This chapter addresses facility safety requirements to provide a suitable operational environment. Such measures seek to ensure that means are adopted to protect staff, visitors, donors, patients, volunteers, and others on the premises.

FACT-JACIE accreditation

General aspects (5)

The basis for FACT-JACIE Cell Therapy accreditation consists of the agency's standards, which address every aspect of the cell-based product's manufacture and application, potentially impacting its quality and patient care.

FACT Standards are the work of renowned experts from several countries committed to furthering progress in cell therapy. The standards are consensus-driven and drafted by specific committees, clinicians, researchers, technicians, and quality experts. The standards have their foundation in proven scientific knowledge or accepted scientific theories. After standards are drafted, the agency releases them for public consultation, after which a revised version is prepared and submitted to the FACT Board of Directors for consideration.

FACT Standards fall into two categories, general and specific. The former comprises the fundamentals applicable to a wide range of cellular therapies, while the latter applies to specific cell therapy programs, such as the hematopoietic cell therapy program.[5,6]

FACT accreditation process (5.6)

The institution applying for accreditation is advised by a FACT office coordinator, who accompanies the entire process. After an on-site inspection and document examination by a team of qualified inspectors, accreditation is granted upon successful fulfillment of the requirements of the FACT Standard applicable to the program under consideration.

FACT's website provides guidelines with the steps to be followed in the accreditation process, which include:

1) Requirement and eligibility check.
2) Appointment of a FACT accreditation coordinator to provide the institution with assistance with questions or concerns during the process.
3) Completing the self-assessment tool and then submitting it to FACT. - The self-assessment tool is a helpful preparatory resource, as it contains all the requirements of the Standard, with questions to be answered by the organization to have its conformity assessed by the accreditation body. An organization that applies for accreditation for the first time has 12 months after the eligibility form approval to prepare all required documentation, adjust their processes, meet FACT Standard requirements, and submit the Compliance Form. For accreditation renewal, the organization must submit the Compliance Form within 11 months before their certificate expires.
4) Before the on-site inspection - after the Compliance Form has been deemed complete by the accreditation coordinator, the necessary adjustments will be made for the on-site inspection.
5) The documentation for inspectors' examination is prepared.
6) On-site inspection.
7) After the on-site inspection, the Accreditation Report, containing a summary of the inspection findings, is prepared for review by FACT towards a decision on accreditation, which, once granted, results in the accredited institution obtaining a certificate, which has a three-year validity period.

Conclusion

Regardless of the accrediting agency of choice, the accreditation process consists of a crucial factor in achieving improved health care for patients and donors. Adherence to quality management principles, data recording, and the use of clinical outcome information is critical to ensure the traceability of processes and all that surrounds them. In addition, quality principles ultimately favor the standardization of protocols and encourage good organizational performance, with the ultimate result of increasing the safety of the entire process from cell therapy product manufacturing to clinical outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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