FACT Guidelines for Histocompatibility Standards and Accreditation Programs

FACT-accredited Clinical Programs and Cord Blood Banks are required to use HLA typing laboratories that are accredited by ASHI, EFI, or another FACT-approved accrediting organization providing histocompatibility services appropriate for hematopoietic cellular therapy transplant patients. This document provides guidelines for evaluating the standards and accreditation program of agencies that wish to be approved by FACT for this service.

A. Facilities

Standards must require facilities that provide at a minimum:

1. Sufficient space for all procedures and analyses to be safely carried out without risk of errors caused by the environment.
2. Immediate access to records required for clinical services.
3. Long-term storage of records, including digital storage, for the duration required by relevant regulations.
4. Appropriate, monitored, and documented temperature-controlled storage immediately available for all reagents and specimens (e.g., freezers and refrigerators).
5. Adequate lighting and ventilation.
6. Uninterruptible or emergency power supplies for essential equipment.
7. Clean and organized facilities to prevent specimen cross-contamination.

B. Laboratory personnel

Any activity can be delegated to an appropriate designee. A designee is an individual with appropriate education, experience, or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility. A single individual may fill more than one role if appropriately credentialed.

Standards must require at a minimum:

1. A Director who meets the following qualifications:
    a. Individual with a medical or doctoral degree with appropriate and adequate experience.
    b. Responsible for the overall operation and administration of the laboratory including:
        i. Accessible to the laboratory to provide on-site direction.
        ii. Responsibility for laboratory compliance with applicable laws, regulations, and accreditation requirements.
        iii. Telephone and electronic consultation commensurate with the workload.
2. A Technical Supervisor who meets the following qualifications:
    a. Individual with a medical or doctoral degree with appropriate and adequate experience.
    b. Responsible for the technical and scientific oversight of the laboratory, including:
        i. Accessible to the laboratory to provide on-site direction.
        ii. Availability during all hours of laboratory operation.
        iii. Telephone and electronic consultation commensurate with the workload.
3. A Clinical Consultant who meets the following qualifications:
    a. Individual with a medical or doctoral degree with appropriate and adequate experience.
    b. Responsible for providing consultation regarding the appropriateness of the testing and clinical interpretation of test results, including:
        i. Accessible to the laboratory to provide on-site direction.
        ii. Available during all hours of laboratory operation.

iii. Telephone and electronic consultation commensurate with the workload.

4. A General Supervisor who meets the following qualifications:
   a. Individual with a medical degree or degree in a relevant science, with adequate experience.
   b. Responsible for day-to-day supervision of testing personnel, reporting of test results, proper performance of all laboratory procedures and reporting of test results in the absence of the laboratory director and technical supervisor.
      i. Accessible to the laboratory to provide on-site direction.
      ii. Available during all hours of laboratory operation.
      iii. Telephone and electronic consultation commensurate with the workload.
5. Sufficient number of additional staff (a minimum of one) to allow for continuous coverage. Staff must:
   a. Possess specified education, training, and experience.
   b. Be competent for the duties performed.
      i. Be responsible for carrying out the scope and volume of work , including dedication of a specified amount of time and effort to the laboratory.
6. Personnel requirements: Assigned responsibilities are to individuals qualified to perform the duties, including for each staff member:
   a. Establishment of initial qualifications.
   b. New employee orientation.
   c. Initial training and retraining when appropriate for all procedures performed, to include a description of minimal trainer qualifications.
   d. Continued competency assessment annually at a minimum.
   e. Defined requirements for continuing education.

C. Laboratory quality management system

Standards must require a laboratory quality management system that includes pre-analytical, analytical, and post-analytical phases. The laboratory quality management system must include at a minimum:

1. A defined organizational structure.
2. Requirements for personnel, including qualifications, training, and competency.
3. Responsibilities, procedures, and resources defined for implementing and managing quality within the laboratory, including all activities contributing directly or indirectly to quality.
4. Systems to ensure compliance with all applicable laws and regulations.
5. Detection, reporting, and corrective action related to adverse events and complaints.
6. Identification, labelling, and tracking of samples and data.
7. Development, implementation, and review of policies and procedures.
8. Continuous process improvements.
9. Creation, review, control, and maintenance of records.
10. Document control system.
11. Analyses of outcomes.
12. Audits of the quality system.
13. Facilities.
14. Materials management.
15. Procedures validation.
16. Equipment qualification, maintenance, and calibration.
17. Safety.
18. Integrity and back-up of information management systems.
19. Emergency and disaster planning.

D. Confidentiality

Standards must require at a minimum:

1. Compliance with applicable laws and regulations related to recipient and donor confidentiality.
2. Policies and procedures to ensure subject confidentiality throughout the entire process.

E. Data integrity and security

Standards must address system security throughout the entire process (including bioinformatics pipeline) including policies and procedures for:

1. Prevention of unauthorized access of data.
2. Limiting data access based on user role.
3. Control of software installation.
4. Internal and External storage and transfer of data maintains subject confidentiality and security.

F. Proficiency testing (external and internal)

Standards must require at a minimum:

1. When available, subscription to an appropriately approved external graded proficiency testing program with an appropriate number of samples tested each year for each of the assays performed.
2. Establishment of alternatives for external proficiency testing when unavailable for assays performed.
3. Proficiency testing requirements must include:
    a. Distribution of proficiency testing samples to all personnel involved in testing.
    b. Samples treated as routine samples, excepting the proficiency testing samples may not be referred to another laboratory.
    c. Laboratory (external) and/or personnel (internal) blinded to the expected results while performing the testing.
    d. Prior to submission deadline, proficiency testing results can not be discussed between laboratories.
    e. Corrective action if accuracy falls below acceptance criteria.
    f. Maintenance of records.
4. Provision of remedial process, including suspension or limitation of accreditation.

G. Equipment: maintenance and calibration

Standards must include at a minimum, procedures for:

1. Initial qualification of equipment and a process to remove equipment from service in the event of malfunction or failure, and to return repaired equipment to service.
2. Use of equipment in a manner that prevents sample mix-ups, contamination, and cross-contamination.
3. A system to uniquely identify and track all critical equipment used for each sample.
4. Placement of equipment in a clean and orderly manner and located to facilitate cleaning, calibration, and maintenance.
5. Verification of compliance with the maintenance schedule daily prior to use.
6. Standardization and calibration of equipment on a regularly scheduled basis and in accordance with the manufacturer's recommendations.
7. Calibration against a traceable standard, if available. If not available, the basis for calibration shall be described and documented.

8. A procedure that addresses actions to take in the event of equipment malfunction or failure.
9. Routine monitoring of equipment for expected functionality.
10. Availability of emergency power for equipment to store critical reagents and samples.

H. Reagents and controls

Standards must require at a minimum:

1. Quality control of reagents, solutions, controls, and calibration materials to ensure sensitivity and specificity.
2. Freedom from contamination and storage under proper conditions.
3. Controls to monitor key stages of each testing method.
4. Records of reagent lots used for clinical test procedures.

I. Specimens

Standards must require at a minimum:

1. Defined criteria for specimens used for testing, including at a minimum:
   a. Sample type.
   b. Collection, including date and requirements.
   c. Identification and labeling.
   d. Quantity and quality.
2. Defined conditions for temporary and long-term storage of specimens.
3. Defined conditions for transport of specimens.
4. Processes for handling specimens found to be acceptable or unacceptable based upon defined criteria.
5. Precise tracing of a specimen and any derivatives throughout the laboratory's processes up to correct reference in the final report and, when applicable, storage in a repository.

J. General testing

Standards must require at a minimum:

1. Standard Operating Procedures governing testing, including at a minimum:
   a. Following manufacturer instructions and validation of any modifications.
   b. Defined sensitivity level, if relevant.
   c. Established criteria for reporting qualitative and/or quantitative results.
   d. Established criteria for accepting or rejecting a result.
   e. Details regarding the test system being utilized and its limitations.
   f. Defined characteristics of the starting material.
   g. Management of notifications from vendors that may affect clinical care.
2. Staff competency for assays performed.
3. Testing and resolution of assays appropriate to the clinical purpose of the testing.
4. Bioinformatics integration with registries and transplant programs (see WMDA bioinformatics document).
5. Validation and/or verification of all testing methods.
6. Requirements for specimen processing, handling, and storage.
7. Requirements for test environment such as instrumentation and temperature.

K. Test systems used for HLA assignment

Standards must include requirements for test systems to be used for HLA assignments. Minimum requirements include:

1. Nucleic acid amplification. Assays involving nucleic acid amplification must:
   a. Be monitored for contamination with previously amplified DNA.
   b. Include precautions taken to avoid and detect contamination.
   c. Address artifacts such as nonspecific or preferential amplification.
2. Alternative HLA typing methods including, but not limited to:
   a. PCR-SSP
   b. PCR-SSOP
   c. DNA sequencing
   d. NGS
3. Controls for each assay type to address technical failures at each stage of the assay and to ensure accurate results.
4. Confirmatory typing of recipient and donors using different samples.
5. Appropriate typing resolution and loci required for donor selection.
6. Use of current nomenclature and resolution of common and intermediate including null alleles when performing high resolution typing.
7. Criteria for retyping by molecular method is required.
8. Identification and resolution of discrepancies in typing results.

L. Test systems for identifying donor-specific antibodies.

Standards must require at a minimum:

1. Assays to detect the presence, specificity, and quantity of antibodies directed toward HLA.
2. Methods for each assay type to address technical failures at each stage of the assay and to ensure accurate results.

M. Test systems for characterizing donor chimerism

Standards must require of laboratories performing chimerism testing at a minimum:

1. The polymorphic nature, chromosome location and independent nature of the marker analyzed must be established.
2. Minimum number of informative markers used in calculation is established.
3. Preferential amplification is considered in the data analysis.
4. Minimum and maximum DNA requirements for optimal sensitivity and specificity and to minimize carry over contamination.
5. Specification of assay conditions and data interpretation when cellular therapy products from multiple donors have been infused.
6. Engraftment analysis using pre-transplant patient and donor samples to identify informative markers among individuals tested.
7. Specification of criteria for reporting percent donor and recipient DNA in mixed chimeric samples.
8. If evaluation of cell subsets is performed, the actual or estimated purity is reported.
9. Appropriate controls to distinguish donor and recipient alleles in each test.
10. Validation of the sensitivity and quantitative accuracy of the amplification based on the number of donors.

N. Requests for testing and reporting of results; Laboratory Agreements with Transplant Centers and Donor Registries

Standards must require at a minimum:

1. A written agreement for services provided between the laboratory and each transplant center and between the laboratory and donor registries that clearly outlines responsibilities.
2. Specification of personnel with the authority to requisition a test.
3. Information that must be provided regarding the sample being tested.
4. Details for communication between the transplant center/registry and the testing laboratory regarding:
    a. How testing will be requested.
    b. Specimen acceptability and rejection.
    c. Methods to be used.
    d. Required resolution of the assay
    e. Limitations of the assay.
    f. How test results will be provided.
5. Inclusion of information on any electronic or physical reports related to:
    a. Ambiguity in test results.
    b. Limitations of the method used in the assay related to the results.
    c. Criteria used to determine a result (e.g., whether population frequencies were used in the final assignment).
    d. Identification of the laboratory and any accreditation or licensing held as required by applicable laws and regulations.
    e. For donor registries, information may be provided for groups of results.
6. Use of World Health Organization (WHO) HLA nomenclature and other widely accepted nomenclature (e.g., multiple allele codes used by hematopoietic progenitor cell registries).
7. Specification of personnel with the authority to receive a test result.
8. How long test results must be retained by the laboratory.

O. Electronic data collection and analysis

Standards must require at a minimum:

1. Validation of software used for analysis of laboratory results in the laboratory before use, after modifications, and periodic verification thereafter.
2. Criteria for level of independent review and interpretation of data.
3. Description of reference database version used to assign HLA types and the frequency with which updates of the database are performed.
4. Provisions for the minimum retention and maintenance of raw data.
5. Records of software versions used for clinical procedures.

P. Accreditation program

The accreditation program must include:

1. Written SOPs for:
    a. The accreditation process.
    b. Notification of changes in key personnel.
    c. Notification of change of physical location of the laboratory.
    d. Performing inspections.
    e. Oversight of the inspection and accreditation processes.
    f. Inspector qualification and training.

2. Inspectors and inspector training to include:
   a. Specific requirements for required education, training, and experience.
   b. Documented technical competency in histocompatibility testing for hematopoietic stem cell transplantation using both related and unrelated donors, including umbilical cord blood.
   c. Competency in the technical areas that will be assessed during an on-site inspection.
   d. Performance during at least one on-site inspection as a trainee.
   e. Training in changes in policies and regulations that can affect a laboratory's compliance via training workshops or self-study programs at regular intervals.
3. Accreditation process to include:
   a. Standards development process that includes input from committee of experts in HLA typing, including expertise related to typing for hematopoietic progenitor cell transplantation.
   b. On-site inspections incorporating a systematic evaluation of compliance with the established standards.
   c. Consistent and thorough process for review of inspection reports.
   d. Methods to monitor effectiveness of the accreditation process and enact corrective actions when necessary.
4. Processes equipped to adapt to new technologies used to meet FACT requirements for loci and resolution, including, but not limited to:
   a. Review of written standards on a regular, defined timeline.
   b. Minimum frequency of accreditation cycles of three years.
   c. Demonstrated ability to adapt to changes.