

## Fast Focus on Compliance: Histocompatibility Checklist Changes and Key Points

### Major Topics Include:

- Procedures and test systems
- Quality management
- Personnel
- Delineation of requirements for specific donor types (hematopoietic progenitor cell versus solid organ)

### Removed Items:

- Requirements for balances and pipettes were moved to the All Common checklist.

### New/Revised Items:

- The items in the table below include one new requirement from the 2018 edition and several significantly revised checklist requirements from the 2019 edition (refer to highlighted text and key points).

Requirement ID	Requirement	Key Points
HSC.20200	<p><b>Procedure Manual</b></p> <p>The procedure manual contains specific instructions for test performance, preparation of reagents, control methods, specimen requirements, limitations of the method, and criteria for accepting/rejecting runs and reporting of results for each of the following procedures, as applicable:</p> <ol style="list-style-type: none"> <li>1. Lymphocyte isolation</li> <li>2. HLA serologic typing</li> <li>3. HLA molecular typing</li> <li>4. Crossmatching T-cells</li> <li>5. Crossmatching B-cells</li> <li>6. Antibody screening and identification</li> <li>7. Engraftment monitoring</li> <li>8. ABO grouping</li> <li>9. Complement titration</li> <li>10. Environmental control</li> </ol>	<p><b>Phase II</b></p> <ul style="list-style-type: none"> <li>• Added more specific information regarding components necessary to include in standard operating procedures added.</li> </ul>

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HSC.21050

## Recipient Sera

Phase II

The most appropriate recipient sera are employed for final crossmatching or final selection of donor.

**Note:** There must be a written policy defining an appropriate specimen to utilize in transplantation or final donor selection that takes into consideration the potential recipient's past pregnancies, past transplants, recent blood transfusions, and sensitization history. The specimens must have been properly handled and appropriately stored to preserve antibody integrity.

### References

- 1) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.
- 2) Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee ISCT and EBMT (JACIE). FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration. 7th Edition, March 2018.

- Added content on final donor selection.

HSC.21275

## Final Report

Phase II

The final report includes the following:

- Summary of the methods used
- Loci tested
- Objective findings
- Limitations of the methods, when applicable
- Interpretation
- List of ambiguous allele combinations and unresolved alleles for high resolution typing, if applicable

**Note:** For donor registries, aggregate reports may be provided for a group of donors.

### References

- 1) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.

- Reformatted and expanded items to be included on the final report to include limitations of the methods.



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HSC.21287

## Result Review

Phase II

All laboratory results (excluding reports from outside referral laboratories) **have two levels of independent review**, including review by the section director (technical supervisor) or designee prior to release.

**Note:** The initial review may be performed by validated automated analysis or by a qualified individual. The data output results must be reviewed by a qualified individual before release.

- Modified to specify two levels of independent review added to the requirement.

HSC.22531

## Alarm System

Phase II

There is an audible alarm for each sample or reagent storage unit, and the alarm is monitored 24 hours per day (in laboratory or remotely).

**Note:** All storage units must have an audible alarm with continuous monitoring (in laboratory or remote). The laboratory **must** be able to demonstrate how this system works, and that there is a process to ensure a timely response to an alarm.

### References

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 2003(Jan 24):[42CFR493.1278(a)(1)].

- Replaced the word “should” with “must” in the Note to clarify expectations.

HSC.28186

## Serologic Typing – Class I

Phase II

Target cells are defined for serological determination of HLA Class I antigens, and selected to permit typing the antigens officially recognized by the WHO Committee for which reagents are readily available.

**Note:** **HLA Typing for all hematopoietic progenitor cell donors and recipients**, and deceased organ donors must be performed by molecular methods. Serological determination of HLA Class I antigens should be performed on T-cells or mononuclear cell preparations. Local serological typing reagents must be supported by appropriate documentation of HLA specificity, using cells of known HLA types. The test must detect WHO recognized specificities.

- Added specific content on hematopoietic progenitor cell donors and recipients added.



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## References

- 1) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.
- 2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 2003(Jan 24):[42CFR493.1278(b)] and [42CFR493.1278(5)(iii)].

HSC.28373

## Serologic Typing – Class II

Phase II

The methodology for serological Class II antigen typing defines the proportion of B-cells needed for optimal testing, and the specificities that are officially recognized by the WHO Committee and for which reagents are readily available.

**Note:** The method should produce at least 80% B-cell enriched preparations. Documentation of B-cell enrichment may not be necessary when procedural techniques already distinguish T- and B-lymphocytes, or when well-characterized antibodies are used that can only discriminate and identify Class II antigens. **HLA typing for all hematopoietic progenitor cell donors** and recipients, and deceased organ donors must be performed by molecular methods.

## References

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 2003(Jan 24):[42CFR493.1278(b)] and [42CFR493.1278(5)(iii)].
- 2) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.

- Added specific content on hematopoietic progenitor cell donors and recipients added.

HSC. 29869

## Final Crossmatch Results Availability

Phase II

There is a **written policy that defines when results** of a final crossmatch are available before transplantation for renal transplant patients and for presensitized extrarenal transplant patients.

**Note:** **Laboratories supporting solid organ transplants must be capable of performing** prospective crossmatches and must have a written policy describing in what situations pre- or post-transplant crossmatching is performed for all types of solid organ transplants. Results of the final crossmatch must be available before a kidney transplant is performed. **The policy**

- Clarified crossmatch provisions for solid organ transplantation.



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for presensitized extrarenal transplant patients must describe if and when crossmatches are performed. Crossmatches may be physical or virtual crossmatches as defined in the policy.

## References

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 1992(Feb 28):7170 [42CFR493.1278(f)].
- 2) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.

HSC.33475

## Antibody Identification/Crossmatching

Phase I

The laboratory has policies and procedures for antibody identification and crossmatching as defined by the transplantation programs supported by the laboratory (includes solid organ and hematopoietic progenitor cell transplantation).

- Removed content limiting the applicability of the requirement to “high risk” patients and added specific content to follow transplant program requirements.

HSC.38060

## HLA Typing Level of Resolution

Phase II

The level of resolution of HLA typing is adequate for the clinical programs, including donor registries, and the type of cell, tissue, or organ to be transplanted and meets the requirements of relevant accrediting agencies.

**Note:** When performing HLA typing of deceased donors for the purpose of organ allocation (kidney, kidney-pancreas, pancreas, or pancreas islet donor transplants) in the United States, all of the following loci are required to be reported: A, B, Bw4, Bw6, C, DRB1, DRB3/4/5, DQA1, DQB1, and DPB1. For all other organs, HLA typing may be performed if required by the transplant program.

For hematopoietic progenitor cell transplant, the laboratory must perform HLA typing at the level of resolution and including the loci required by the agreements with the transplant center and/or donor registry.

- Added detailed information regarding level of HLA typing has been added to the checklist item and Note.



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## References

- 1) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.
- 2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 2003(Jan 24):7170 [42CFR493.1278(b)(2)].
- 3) Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee ISCT and EBMT (JACIE). FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration. 7th Edition, March 2018.
- 4) National Marrow Donor Program (NMDP)/Be The Match. US Transplant Center Participation Criteria. Document #A00228. Revised 2017.

HSC.38097

## Sequence-Based Typing

## Phase II

For sequence based typing, there are records of the following:

- Templates with sufficient specificity for a locus or allele
- Appropriate monitoring of all steps
- Adequate electrophoretogram quality to support the sequence results
- Definition of a sequence following a procedure for accurate assignment of HLA alleles

**Note:** Records must include the HLA locus and allele specificity of the template, the source of the sequence data base used (annually updated), and procedures to resolve ambiguous combinations. Assignment of alleles for HLA loci must be done by comparing the sequences obtained by nucleotide assignment with the sequences of all alleles that are recognized by the WHO. Current databases of known sequences for all WHO-recognized alleles must be immediately available.

Laboratories must recognize and report ambiguous allele combination(s) and resolve these as appropriate for the clinical use as defined by the transplant agreement. Alternative ambiguous allele combinations must be resolved when the alternatives include more than one common and well-documented allele type (Cano et al. Human Immunology 2007 or Mack et al, HLA 2013).

- Updated and reformatted content to clarify records to be maintained for sequence-based typing. Added new content on ambiguous allele combinations to the Note.



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HSC.38150

## Sensitivity Control

Phase II

A sensitivity control is used and evaluated with each run.

**Note:** A low positive control may be used to meet this requirement.

- Added Note to address frequent participant questions.

HSC.38190

## Cell Subset Purity

Phase II

If cell subset enrichment is performed, the patient report includes the actual or approximate purity of the cell subset.

**Note:** The determination of the actual or approximate purity of the cell subset does not imply that the purity determined in validation studies can be used without further evaluation. An actual measurement may be performed at the time of sample testing. Some isolation methods and cell subpopulations (eg, CD56) may not produce enough cells to test purity and run the monitoring engraftment test. At a minimum, the purity can be determined for each lot of reagent used to isolate the cell subset and then be reported as an approximate purity for that specific lot.

- Added requirement in the 2018 edition.

HSC.38845

## HLA Identity Confirmation for Hematopoietic Progenitor Cell Transplantation

Phase II

HLA identity is confirmed in both donor and recipient hematopoietic progenitor cell transplantation.

**Note:** This can be accomplished by molecular HLA allele determination for Class I and II. For NMDP a separate sample is required for confirmatory testing.

For laboratories performing typing to support hematopoietic progenitor cell (HPC) transplantation, repeat HLA typing of the transplant patient using a new sample is performed to verify the individual's HLA type prior to final donor selection for both related and unrelated transplants. Similarly, repeat HLA typing of the related or unrelated HPC donor is performed using a new sample prior to HPC collection. For purposes of verification testing, results from donor registry or another laboratory is acceptable as the first of the two samples required.

- Expanded to address donor and recipient HPC transplantation and added information to the Note to verify the individual's HLA type prior to transplantation for laboratories supporting HPC transplantation.



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Lower resolution is acceptable for one of the two samples as long as the laboratory can document concordance between the two samples.

## Evidence of Compliance:

Written procedure defining confirmation method(s) used for HLA identity.

## References

Nunes E, Heslop H, Fernandez-Vina M, et al. Definitions of histocompatibility typing terms: Harmonization of Histocompatibility Typing Terms Working Group. *Hum Immunol*. 2011 Dec;72(12):1214-6.

HSC.39032

## Haplotype Reporting

Phase II

Haplotype assignments are supported by sufficient evidence.

**Note:** When reporting haplotypes, homozygosity, blanks, recombination, or other genetic information, there must be sufficient evidence from family studies to support such conclusions. If probable haplotypes are reported, the report must indicate clearly that they are “probable.” Reliable haplotype frequencies of the appropriate ethnic groups must be used.

If haplotypes are assigned, this can be done by testing both the parents or clearly defined segregation of the four haplotypes or may be based upon population frequencies. Haplotype assignments based on population frequency, must be clearly stated on the report and include the relevant source (including the version) or reference.

- Added more information to the Note regarding haplotype assignments.



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HSC.39430

## Written Agreements

## Phase II

There are written agreements for histocompatibility testing with each transplant program, organ procurement organization (OPO), or donor registry served by the laboratory, unless clinical urgency prevents such an agreement.

**Note:** Written agreements must be reviewed **biennially** by the histocompatibility section director/technical supervisor, and/or clinical consultant, and the clinical transplant program director, and be revised as necessary.

The agreement with transplant programs, OPOs, and donor registries must include the following:

- Specimen requirements for typing and crossmatching
- **Methods to be used**
- **Limitations of the methods**
- Loci and level of resolution typed
- Process for requesting extended HLA typing
- Process for reporting HLA typing results
- **Process for resolving HLA discrepancies, ambiguities, and errors**
- **Turnaround time from samples receipt to reporting to transplant program, OPO, or donor registry**
- Length of specimen retention for repeat or future testing

If the laboratory supports a program or donor registry that is accepted through the Foundation for the Accreditation of Cellular Therapy (FACT), the agreements must contain the requirements defined in the 6th edition of the FACT Standards.

If a laboratory supports a program or donor registry that is participating in the National Marrow Donor Program (NMDP)/Be The Match, the agreement must contain the provisions defined in the November 2017 NMDP U.S. Transplant Center Participation Criteria.

If the laboratory participates as a member of the United Network for Organ Sharing (UNOS), the written agreements must address all elements defined in the most current version of the Organ Procurement and Transplantation Network (OPTN) Bylaws. Agreements with transplant programs must also include the following:

- Process for reporting and verifying HLA and other data at the time of registration on the waiting list and where there are changes
- Process to obtain sensitization history
- Frequency of periodic sample collection
- Frequency for antibody screening

- Changed review requirement of written agreements from annually to biennially and added additional bullets to agreement requirements.



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- Criteria for crossmatch
- Assay format used for antibody screening and crossmatching
- Criteria for determining unacceptable antigens used during organ allocation
- Protocol for monitoring antibody levels if desensitization is used
- Process for blood type verification if the laboratory registers candidates for the transplant program
- Protocol for monitoring antibody levels if post-transplant monitoring is performed

Agreements with OPOs must also include the following:

- Process for prioritizing donors for histocompatibility testing
- All methods used for crossmatching, interpretation, and reporting of results if crossmatching is done by the OPO

## References

- 1) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.
- 2) Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee ISCT and EBMT (JACIE). FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration. 7th Edition, March 2018.
- 3) National Marrow Donor Program (NMDP)/Be The Match. US Transplant Center Participation Criteria. Document #A00228. Revised 2017.



# Fast Focus on Compliance: Histocompatibility Checklist Changes and Key Points

## HSC.40000

### Section Director/Technical Supervisor Qualifications

### Phase II

The section director (technical supervisor) of the histocompatibility section has the following qualifications.

1. MD or DO licensed to practice (if required) in the jurisdiction where the laboratory is located, or doctoral degree in chemical, physical, biological or clinical laboratory science from an accredited institution, AND
2. Laboratory training and experience: four years training and experience in histocompatibility, or two years training and experience in general immunology plus two years in histocompatibility. For section director/technical supervisors supporting solid organ and/or hematopoietic progenitor cell transplantation, records of training or relevant experience in histocompatibility appropriate to the supported transplant program(s).

**Note:** If there has been a change in the HLA Section Director (Technical Supervisor) in the last two years, the inspector must review the new section director's curriculum vitae and portfolio. **The review should include at least 10 solid organ transplant cases from the portfolio for a laboratory supporting a solid organ transplant program and at least 10 hematopoietic progenitor cell transplant cases representative of the program mix of related and unrelated transplants for a laboratory supporting hematopoietic progenitor cell transplantation.**

If more stringent state or local regulations are in place for supervisory qualifications, including requirements for state licensure, they must be followed.

#### Evidence of Compliance:

- ✓ Records of section director/technical supervisor qualifications including diploma, transcript(s), primary source verification report, equivalency evaluation, board certification, or current license (if required) **AND**
- ✓ Work history in related field.

#### References

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. Fed Register. 1992(Feb 28):7180 [42CFR493.1449(o)].
- 2) Organ Procurement and Transplantation Network (OPTN) Bylaws. Appendix C. Membership Requirements for Histocompatibility Laboratories. US Department of Health and Human Services. November 20, 2018.

- Added separate criteria for evaluating HLA section directors for HPC laboratories.



# Fast Focus on Compliance: Histocompatibility Checklist Changes and Key Points

## Scenario 1

You are inspecting a histocompatibility laboratory. A kidney transplant procedure is scheduled for that day. The transplant recipient has been paired with a living renal allograft donor (sibling) and preliminary crossmatch results for B- and T-cells performed four weeks prior were reported as crossmatch negative using flow cytometry. A repeat crossmatch using the same methodology is performed while you are inspecting and is also found to be negative. The recipient has no sensitizing events and has no detectable HLA antibodies. Immediately after completion of this second crossmatch, the renal transplant coordinator is calling the performing medical technologist for a copy of the results. The technologist releases the results.

What would you do regarding HSC.21287?

- A. Cite the laboratory
- B. Move on, the laboratory is in compliance
- C. Recommend the laboratory implement two levels of independent review into its policy

## Scenario 2

You are inspecting a histocompatibility laboratory. A kidney transplant procedure is scheduled for that day. The transplant recipient has been paired with a living renal allograft donor (sibling) and preliminary crossmatch results for B- and T-cells performed four weeks prior were reported as crossmatch negative using flow cytometry. A repeat crossmatch using the same methodology is performed while you are inspecting but is not released/available prior to the time the transplantation occurs.

What would you do regarding HSC.29869?

- A. Cite the laboratory
- B. Move on, HSC.29869 would only be an issue for extrarenal transplants
- C. Request the laboratory's policy regarding specific protocols and criteria that may permit this action

Scroll to the next page for the correct answers.



# Fast Focus on Compliance: Histocompatibility Checklist Changes and Key Points

## Scenario 1

**The correct answer is A.** Per HSC.21287, it cannot be released. All laboratory results (excluding reports from outside referral laboratories) must have two levels of independent review, including review by the section director (technical supervisor) or designee prior to release.

Note: The initial review may be performed by validated automated analysis or by a qualified individual. The data output results must be reviewed by a qualified individual before release.

## Scenario 2

**The correct answer is A.** Per HSC.29869, for renal transplantation the results of a final crossmatch must be released prior to transplantation. For extrarenal transplants such as living donor liver transplant, the ability to initiate transplantation before release of final crossmatch results is allowed only if there are specific protocols and criteria that are documented as being met that permit this action.

