Proposed Histocompatibility Standards – Comments and Responses

Proposed Standards were made available to New York State permitted laboratories and laboratories in application for a permit on March 4th, 2020. The announcement was by e-mail to the facility and laboratory contact person's e-mail address and the Proposed Standards were posted to the CLEP website.

The comment period ended June 15th, 2020. Comments received from any regulated parties and responses are shown here.

Standards will be adopted July 13th, 2020, with an effective date of August 1st, 2020.

General Histocompatibility Standards Comments

COMMENT:

- The New York State requirements do not align with ASHI requirements. It would be helpful that the state speaks with ASHI before the next revision to the standard.

RESPONSE:

New York State Clinical Laboratory Standards of practice must be substantially equivalent to federal CMS regulations under CLIA. Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. The current Histocompatibility Standards address CLIA regulation, as required. Future revisions to these standards may incorporate requirements for histocompatibility testing from other accreditation programs.

Histocompatibility Standards Comments

Histocompatibility

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 1 (HC S1): Test Procedure In addition to the requirements in Test Procedure Content Standard of Practice 1, the laboratory must have a standard operating procedure that includes, as applicable: a) the preparation of cells or cellular extracts (for example, solubilized antigens and nucleic acids), as applicable to the human leukocyte antigen (HLA) typing technique(s) performed; b) the preparation and/or selection of typing reagents, whether locally or commercially prepared~~, and verification of reactivity~~; c) the policy for antigen redefinition and retyping, including, where applicable, the updating of results and issuance of amended reports; d) a protocol for ensuring that reagents used for typing are adequate to define all clinically relevant loci, at minimum, all HLA-A, B and DR specificities that are officially recognized by the most recent W.H.O. Committee on Nomenclature and for which reagents are readily available; and e) criteria for the assignment of HLA ~~antigens~~ type.	

Histocompatibility Standard 1 (HC S1): Test Procedure

COMMENT 1:

Section b) refers to selection/preparation of typing reagents, commercially or locally prepared. Virtually all HLA typing is performed by molecular techniques at this point, and the verification of reactivity is a holdover from verifying antibody reactivity in serological methods. Standard QC would apply to verifying DNA typing material so this seems superfluous.

Section d: Requires a protocol ensuring reagents for typing to define ALL HLA-A,B,DR specificities recognized by WHO. First, all UNOS and NMDP transplant protocols now require extended typing for both Class I and II loci. Second, as of this writing, there are 26,214 recognized HLA specificities. As written this misses the mark on both points. Please consider including all loci that are of clinical relevance (even disease association and pharmacogenomics), that is Class I – A,B,C and Class II DR/DQ/DP. Perhaps you might require the ability to type at serologic equivalent by WHO (http://hla.alleles.org/antigens/recognised_serology.html).

RESPONSE 1:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 Standard: Histocompatibility (b)(5)(i-v). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. Requirements under (b) and (d) of the standard have been revised based on the comment received.

COMMENT 2:

HC S1 d) - Why only HLA-A, B and DR? We type for Cw, DQ and DP also.
HC S1 e) - Since most typing is done by DNA methods, we rarely assign HLA antigens

RESPONSE 2:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 Standard: Histocompatibility (b)(5)(i-v). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. Requirements under (d) and (e) of the standard have been revised based on the comment received.

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 2 (HC S2): Human Leukocyte Antigen Typing The laboratory must, as applicable: a) use a technique(s) that is established to optimally define, as applicable, human leukocyte antigen (HLA) Class I and II specificities; b) check each HLA typing by testing at minimum: i. a positive control; ii. a negative control material in which, if applicable to the technique performed, cell viability at the end of incubation is sufficient to permit accurate interpretation of results: a. in assays in which cell viability is not required, the negative control result must be sufficiently different from the positive control result to permit accurate interpretation of results; iii. positive control materials for specific cell types when applicable (T cells, B cells, and monocytes); c) if the laboratory uses immunologic reagents (e.g. antibodies, antibody-coated beads) to facilitate or enhance the isolation of lymphocytes, or lymphocyte subsets, the efficacy of the methods must be monitored with appropriate quality control procedures; d) if reagent typing sera is prepared in-house, the inventory must indicate the source, bleeding date,	

Histocompatibility	
Proposed Standard	***Proposed Guidance***
identification number, reagent specificity and volume remaining; e) use HLA antigen terminology that conforms to the latest report of the World Health Organization (W.H.O) Committee on nomenclature; potential new antigens not yet approved by this committee must have a designation that cannot be confused with W.H.O. terminology.	

Histocompatibility Standard of Practice 2 (HC S2): Human Leukocyte Antigen Typing

COMMENT:

a) Requires optimal technique to define, but…..
b) – d) Refer to requirements for serological typing, which if performed is in direct conflict to section a. Any HLA reporting clinical testing should be using molecular methods, yet no reference to this being an appropriate method for HLA is even addressed!
e) references WHO nomenclature again, and is covered under HCS1 d.

RESPONSE:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 (a)(3)(4) and (b)(1), (4) and (6)(i-iii). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. There is no change to the standard based on the comment received.

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 3 (HC S3): Human Leukocyte Antigen Antibody Screening The laboratory must, as applicable: a) use a technique that detects human leukocyte antigen (HLA) specific antibody with a specificity that is equivalent or superior to that of the basic complement-dependent microlymphocytotoxicity assay; b) use a method that distinguishes antibodies to HLA Class II antigens from antibodies to Class I antigens to detect antibodies to HLA Class II antigens; c) use a cell panel that contains all major HLA specificities and common splits or, if the laboratory does not use commercial panels, it must maintain a list of individuals for fresh panel bleeding; and d) check each antibody screening test using, at minimum: i. a positive control material containing antibodies of the appropriate isotype for the assay; and ii. a negative control material.	

Histocompatibility Standard of Practice 3 (HC S3): Human Leukocyte Antigen Antibody Screening

COMMENT 1:

This section again implies that the standard method is complement-dependent + augmented version. Section c addresses commercial panels and if not used the lab MUST maintain a list of individuals for fresh panel. This is amazingly out of date. Very few labs do cell-based antibody testing. Both UNOS and ASHI require a solid phase assay for transplantation. This entire section as it stands is not in keeping with current clinical practice.

RESPONSE 1:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 (d)(1-3) and (6)(i-ii). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. There is no change to the standard based on the comment received.

COMMENT 2:

HC S3 c) - This is really, really outdated and completely ignores the solid phase microbead array antibody screening and identification testing that has been our primary method for at least the last 10-15 years.

RESPONSE 2:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 (d)(1-3) and (6)(i-ii). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. There is no change to the standard based on the comment received.

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 4 (HC S4): Transplantation If a laboratory provides histocompatibility testing for a transplantation, the laboratory must, as applicable: a) HLA type all potential transplant ~~beneficiaries~~ recipients at a level appropriate to support clinical transplant protocol and donor selection; b) HLA type cells from organ donors referred to the laboratory; c) have available and follow a written policy that requires screening potential transplant ~~beneficiaries~~ recipients	a) The laboratory should make a reasonable attempt to have available monthly serum specimens for all potential transplant beneficiaries for periodic antibody screening and crossmatching.

for preformed HLA-specific antibodies at a frequency consistent with clinical transplant protocols;

d) have available and follow written criteria and procedures for antibody identification to the level appropriate to support clinical transplant protocol;

~~e) periodically perform antibody screening and crossmatching in potential transplant beneficiaries;~~

f) have and follow policies and protocols specifying the histocompatibility testing (i.e., HLA typing, antibody screening, crossmatching) to be performed for each type of cell, tissue or organs to be transfused or transplanted with policies that must include, as applicable:

i. testing protocols for ~~cadaver~~ deceased donor, living, ~~living-related~~ and combined organ ~~and tissue~~ transplants;

ii. testing protocols for patients at high risk for allograft rejection; and

iii. the level of testing required to support clinical transplant protocols (e.g., antigen or allele-level typing);

g) for renal ~~allo~~transplantation and combined organ ~~and tissue~~ transplant in which a kidney is to be transplanted, have available results of final crossmatches before the kidney is transplanted.~~; and~~

~~h) for nonrenal transplantation, if HLA testing and final cross matches were not performed prospectively because of an emergency situation, the laboratory must document the circumstances, if known, under which the emergency transplant was performed, and record of the transplant must reflect any information provided to the laboratory by the patient's physician.~~

Histocompatibility Standard of Practice 4 (HC S4): Transplantation

COMMENT 1:

The term "transplant beneficiaries" is odd. These are recipient, but transplant is not an entitlement program. In section f, the term "cadaver donor" is also used. The appropriate term is deceased donor. These standards do seem to have had some updating at least. Section g) refers to the final crossmatch and there must be discussion about the type of crossmatch that may be used. The other standards do address the need for supporting the clinical program. As part of that many/most labs now use a paper or "virtual" crossmatch, at least for recipients who are not allosensitized. The reason for this is to limit or eliminate the cold ischemic time accrued by organs that have been procured. Each hour of cold ischemia increases the risk of allograft failure and death. There are multiple publications on this topic that should be considered. An immunological assessment prior to transplant is very important, but requiring the transplant to be held up for a physical test, especially in a patient for whom no antibody is detected is actually harmful. Frankly, I would advise friends and family to seek listing elsewhere if this is maintained. The same basically applies to section h). Cardiac transplantation is, by nature, emergent and requiring documenting this for every case carries no benefit.

RESPONSE 1:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 (b)(2)(3), (d)(4)(5)(7), and (f)(1-3). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. The standard has been revised based on the comment received.

COMMENT 2:

HC S4 a) - Transplant recipients are recipients, not beneficiaries. It's not a life insurance policy. Everyone else, including UNOS, calls them recipients. Changing what they are called only adds to confusion. This word is used in other standards as well. Please change it to recipients in all of them.

HC S4 e) – How do you expect labs to periodically perform crossmatching in all potential transplant ~~beneficiaries~~ **recipients**? We can only do crossmatching when there's a donor for them. Periodic implies a set schedule. We can do that for antibody screening but not for crossmatching.

HC S4 f)i. – The current accepted terminology is **deceased** donors, not cadaver. There is no need to make living-related a separate category from living. And what do you mean by combined organ and tissue transplants? Do you mean a composite tissue allograft? That is very different and doesn't involve an organ. If that's not what you mean, please give an example of a combined organ and tissue transplant in the guidelines.

HC S4 g) – Do you mean a physical final crossmatch or is a virtual crossmatch acceptable? You need to specify because a lot of programs are going to transplant with a virtual crossmatch. Also, there's no need to specify renal allotransplantation since you're not going to do an auto or xeno renal transplant.

HC S4 h) – Almost all liver and most heart transplants happen without crossmatches. They're not necessarily emergencies and it would be onerous for the lab to have to document the circumstances each time. It's not up to the lab anyway. If someone needs to document it, it should be the transplant program. But again, this is why you need to have standards regarding virtual crossmatches because that's what's being done.

HC S4 guidance d) – This guidance doesn't make sense for standard HC S4 d). It does make more sense for HC S4 c). Perhaps that's what you meant? But I do think you should be careful with saying things like "make a reasonable attempt" because everyone defines that differently and the person actually having to do the work is going to define it very loosely.

RESPONSE 2:

The Standard is consistent with requirements in federal CMS regulation CLIA 493.1278 (b)(2)(3), (d)(4)(5)(7), and (f)(1-3). Laboratories seeking or holding a New York State Clinical Laboratory Permit must comply with all applicable standards. The standard has been revised and guidance removed based on the comment received.

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 5 (HC S5): Crossmatching The laboratory must, as applicable: a) use a technique(s) documented to have increased sensitivity in comparison with the basic complement-dependent microlymphocytotoxicity assay; b) have available and follow written criteria for:	

i. selecting appropriate patient serum samples for crossmatching; ii. the preparation of donor cells or cellular extracts as applicable to the crossmatching techniques performed; and c) ~~check each crossmatch for HLA Class II antigenic differences using~~ select appropriate control~~s materials~~ to monitor ~~test components and each phase of~~ the test system to ensure acceptable performance.	

Histocompatibility Standard of Practice 5 (HC S5): Crossmatching

COMMENT:

HC S5 c) – I have absolutely no idea what this standard is asking for. I can't even offer suggestions to improve it because it makes no sense to me.

RESPONSE:

The Standard is consistent with requirements in federal CMS regulation CLIA 493.1278 Standard: Histocompatibility (e)(1), (2)(i)(ii), and (3). The standard has been revised based on the comment received.

Histocompatibility	
Proposed Standard	***Proposed Guidance***
Histocompatibility Standard of Practice 6 (HC S6): Environmental Temperature Monitoring Refrigerators and freezers must be monitored to ensure storage temperatures are maintained for each type of specimen (donor and recipient ~~beneficiary~~) and reagent. The laboratory must:	

a) use a central or audible temperature alarm system to monitor storage temperatures; b) have a documented plan for alternative storage for an emergency or a refrigerator or freezer failure; and c) a system to easily retrieve specimens.	

Histocompatibility Standard of Practice 6 (HC S6): Environmental Temperature Monitoring

COMMENT:

HC S6 – Refrigerator and freezer temperatures and alarms are covered in the general standards. Why repeat them here? You could just say that donor and ~~beneficiary~~ **recipient** samples must be maintained at appropriate temperatures and the lab must have a system to easily retrieve them."

RESPONSE:

The standard is consistent with requirements in federal CMS regulation CLIA 493.1278 Standard: Histocompatibility (a)(1) and (2). These requirements are specific to histocompatibility testing and more stringent than the General Systems Standards. The term recipient has been added to the standard based on the comment received.