



CLIAC Waiver Discussion

February 2004



CLIAC Charge Waiver

- **Convene a Workgroup**
- **Review Workgroup findings at February meeting**
- **As appropriate, recommend to HHS**
 - **Changes to the waiver process**
 - **Oversight of waived testing**



CLIAC Process

- **Consider the Workgroup's findings for each issue**
- **Clarify or revise the issues addressed in the findings**
- **Provide recommendations**



Waiver Issues for Discussion

- **Study(ies)-sites, participants, samples, duration, evaluation of test performance**
- **Specimen characteristics**
- **Test system characteristics-flex studies**
- **Labeling-test system instructions and limitations, intended use**
- **Fail-safe, failure-alert mechanism(s)**
- **Quality control**
- **Sales restrictions**
- **Post-waiver surveillance**



Waiver Studies

Workgroup agreed studies should demonstrate likely test performance in actual clinical use by including

- Intended clinical testing sites**
- Intended users as study participants**
- Intended sample type/matrix whenever possible**
- Testing over time as in typical clinical testing**



Waiver Studies

Workgroup agreed

- **One study may be used to demonstrate test performance (accuracy and precision)**
- **Study should provide statistically valid comparison of waived test to a well-documented, traceable test method**



Waiver Studies

Workgroup agreed waiver guidance should include references for evaluating test methodology, such as

- NCCLS EP-12A: User Protocol for Evaluation of Qualitative Test Performance**
- NCCLS EP21-A: Estimation of Total Analytical Error for Clinical Laboratory Methods**



Waiver Studies

Workgroup suggested waiver guidance should

- Address statistically valid sample sizes relative to prevalence**
- Include examples of statistical methods for evaluating study data**



Waiver Studies

CLIAC Discussion and Recommendations



Specimen Characteristics

Workgroup expressed concerns about

- Expansion of specimen types that require pre-analytic steps including
 - Manipulation/processing
 - Interpretation/judgment of specimen quality/integrity
- Plasma and serum that may be error-prone due to manipulation, centrifugation
- Specimen types including stool, sputum, swabs other than throat



Specimen Characteristics

Workgroup noted that if specimen types are expanded, waiver studies need to

- Include the same specimen handling and processing as intended users in clinical use**
- Demonstrate test performance is not affected by specimen type, handling or processing**



Specimen Characteristics

CLIAC Discussion and Recommendations



Test System Characteristics

**Workgroup agreed waived tests
should provide**

- Direct read-out of results
(quantitative) or**
- Distinct positive/negative
endpoint (qualitative)**



Test System Characteristics

For test systems with distinct color gradations, Workgroup agreed

- **Studies by intended users should demonstrate**
 - **Comparable performance to a traceable reference method**
 - **Interpretation of color gradations does not affect accuracy of test reading**
- **Labeling should include a warning when color-blindness could affect reading test results**



Test System Characteristics

CLIAC Discussion and Recommendations



Flex Studies

Workgroup agreed

- **Waived tests may need to be more robust than non-waived tests**
 - **Potential sources of error need to be identified and studies should demonstrate that sources of error are controlled or mitigated**
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Flex Studies

Workgroup agreed

- **As part of the waiver submission, manufacturers should include information on**
 - Risk assessment
 - Likelihood of erroneous results
 - Risk mitigation measures taken
- **Risk assessment/mitigation information should be part of the test system labeling**



Flex Studies

CLIAC Discussion and Recommendations



Labeling - Test System Instructions

Workgroup agreed

- **Test system labeling format should be standardized**
- **Labeling for newly waived test systems should**
 - **Identify the test system as waived**
 - **Include results of waiver studies**
 - **Include a quick reference guide**



Labeling - Test System Instructions

Workgroup agreed

- **Waived test system instructions need to be**
 - **Clear**
 - **Easy to understand**
 - **Readable font**
 - **Written at no higher than 7th grade level**
- **Instructions should include specific elements concerning test performance, labeling limitations, fail-safe/failure-alert mechanisms, and quality control**



Labeling - Test System Instructions

Workgroup agreed

- **Test systems waived based on home-use approval need to include a cautionary statement that no accuracy and precision studies have been performed to support use in a clinical setting, unless data is provided to show otherwise**



Labeling - Test System Instructions

CLIAC Discussion and Recommendations



Labeling - Limitations & Intended Use

Workgroup agreed

- Context of testing and clinical impact should be considered when making decisions about waived test limitations and intended use
- Limitations, restrictions and special considerations should be included in test system instructions and quick reference instructions



Labeling - Limitations & Intended Use

Workgroup agreed

- Major limitations need to be prominently displayed on the outside of test packaging
- Labeling needs to include a warning that failure to adhere to limitations/intended use instructions is off-label use resulting in the test being uncategorized, high complexity and subject to all CLIA regulations



Labeling - Limitations & Intended Use

Workgroup acknowledged that manufacturers

- **May not be able to include all limitations on the outside labeling**
- **May not be able to limit the distribution of a test as specified in intended use**



Labeling - Limitations & Intended Use

CLIAC Discussion and Recommendations



Fail-safe Mechanisms

Workgroup agreed

- **Fail-safe mechanisms ensure that a waived test system does not provide a result (lock-out) if the result exceeds the reportable range or any component malfunctions**
- **Lock-out features are the ideal fail-safe mechanism, but may not always be feasible**
- **Risk mitigation may serve as a failure-alert when fail-safe mechanisms are not feasible**



Failure-alert Mechanisms

Workgroup agreed

- In lieu of a fail-safe, failure-alert mechanisms are critical and should be used to notify the operator of test system problems
- Manufacturers should provide built-in checks or QC materials whenever feasible



Failure-alert Mechanisms

Workgroup agreed if some components of waived test systems are not monitored internally

- **Electronic checks, when available, should be performed at specified intervals**
- **External QC should be tested to monitor**
 - **Operator performance**
 - **Test system operation**
 - **Environmental conditions (e.g. temperature, humidity)**



Fail-safe/Failure Alert Mechanisms

CLIAC Discussion and Recommendations



Quality Control

Workgroup agreed for external QC testing

- Regulatory guidance should address minimum frequency based on studies
- Manufacturers should
 - Determine minimum frequency based on risk assessment and risk mitigation
 - Specify minimum frequency in test system instructions
 - Provide recommended levels of QC materials appropriate for medical decisions



Quality Control

Workgroup agreed

- **QC materials should be**
 - **Provided with, not necessarily in, test kits to increase the likelihood of QC testing**
 - **Ready to use or require only simple preparation**
- **When QC materials are not provided, manufacturer should recommend sources for QC materials in the package insert**



Quality Control

CLIAC Discussion and Recommendations



Waiver Sales Restrictions/ Best Laboratory Practices

- **Workgroup agreed some waived tests may require sales restrictions**
- **Workgroup suggested**
 - **Some of the proposed "sales restrictions" could be better addressed as "best laboratory practices" for laboratories performing waived tests**
 - **Development and promotion of "best laboratory practices" guidelines for training/education of waived laboratories**



Waiver Sales Restrictions/ Best Practices

CLIAC Discussion and Recommendations



Post-waiver Surveillance

- **Workgroup noted surveillance of waived tests is needed and is**
 - **Preferable to passive event reporting to FDA by manufacturers**
 - **Especially critical in waived laboratories with no system of monitoring test performance**
 - **The shared responsibility of manufacturers, laboratories and government**
- **Specific plans for post-waiver surveillance were not defined**



Post-waiver
Surveillance

CLIAC Discussion and Recommendations
