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**

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 uncatorized, 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**

CLIAC Discussion and Recommendations

Waiver Sales Restrictions/ Best Laboratory Practices

- **Workgroup agreed <u>some</u> 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**

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