



Waiver Workgroup
Report to CLIAC
February 11, 2004



Waiver Workgroup Charge

Waiver Workgroup is to

- Review waiver data**
- Review stakeholder concerns**
- Recommend to CLIAC**
 - Changes to the waiver process**
 - Oversight of waived testing**
- Report at the February 2004 CLIAC meeting**



Waiver Workgroup Process

• January 16, 2004 Meeting

• Workgroup participants:

- Physicians who use waived tests
 - Clinical laboratory professionals
 - Manufacturers
 - Public health laboratory professionals
 - Government agency representatives
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Waiver Workgroup Members

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Waiver Workgroup Process

- **To stimulate discussion, workgroup considered proposals based on:**
 - **Previous CLIAC recommendations**
 - **AdvaMed proposal**
 - **Waiver proposed rule**
 - **FDA guidance**
- **Consensus not required**
- **Lively discussion produced recommendations**



Issues Considered by the Workgroup

- **Studies to support waiver**
 - Sites
 - Participants
 - Samples
 - Duration
 - Statistical analysis
- **Specimen characteristics**



Issues Considered by the Workgroup

• Test system characteristics

- Flex studies

• Labeling

- Test system instructions
 - Limitations and intended use
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Issues Considered by the Workgroup

- **Fail-safe, failure-alert mechanisms**
- **Quality control**
- **Sales restrictions**
- **Post-waiver surveillance**



Waiver Studies Proposal

• Duplicate actual intended use

• Intended clinical testing sites

- POLs, ERs, outreach sites, health fairs, etc.

• Intended users

- Personnel from POLs, ERs, and other typical waived testing sites

• Intended specimen type

- Fresh specimens
- Authentic specimen matrix

• Testing over several days



Waiver Studies Proposal

- **Compare proposed waived test to a valid comparison standard**
- **Traceability of comparison method**
- **Statistical validity of comparison**
 - **Comparable performance within sites, between sites, among sites**
 - **Adequate number of specimens for disease/analyte**
 - **Special considerations for low prevalence diseases – include adequate positive, negative specimens**



Waiver Studies Proposal

- **One study may demonstrate test performance**
 - **Accuracy and precision**
 - **Example: two-armed trial of duplicate or split samples**



Waiver Studies Proposal

● **References for evaluating test methodology**

- **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 Discussion

- **Agreed with proposal**
 - **Waiver guidance should address**
 - **Statistically valid sample sizes**
 - **Choice of statistical methods for evaluating data**
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Specimen Characteristics Proposal

- **Current waived test specimens include**
 - **Capillary whole blood**
 - **Urine**
 - **Throat swabs**
 - **Saliva/oral fluid**
 - **Tissue biopsies**



Specimen Characteristics Proposal

• New types of specimens require studies that demonstrate

- Intended users can consistently perform correct specimen handling, processing
 - Intended users can consistently perform required manipulations
 - Test performance and results are not affected by specimen type or handling, processing
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Specimen Characteristics Workgroup Discussion

- **Concerns were expressed about expansion of waived test specimen types, particularly specimens requiring**
 - **Pre-analytical manipulation/processing**
 - **Interpretation/judgment of specimen integrity**



Specimen Characteristics Workgroup Discussion

- **Plasma and serum were considered as potential waived test specimen types, but were not supported by some due to specimen manipulation/centrifugation processes which are complex, error-prone**



Specimen Characteristics Workgroup Discussion

- **Concerns were raised about appropriateness of other types of specimens for waived tests. Examples include**
 - **Stool specimens**
 - **Sputum**
 - **Swabs other than throat swabs**



Specimen Characteristics Workgroup Discussion

- **Workgroup advocated caution in**
 - **Considering other specimen types**
 - **Allowing manipulation of waived test specimens**
- **Expansion of specimen types should occur only if studies demonstrate test performance is not affected**



Test System Characteristics Proposal

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- **Waived tests should provide**
 - **Direct read-out of results (quantitative tests) or**
 - **Distinct positive/negative endpoint (qualitative tests)**
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Test System Characteristics Proposal

- **Test systems with distinct color gradations should be considered for waiver only when studies demonstrate test performance, by intended users, is comparable to a traceable reference method**
- **The adequacy of any test system should be based on valid, empirical data**



Test System Characteristics Workgroup Discussion

- **Studies should demonstrate that the interpretation of color gradations is not a factor in accurate test reading**
- **Concerns were raised about color-blind individuals reading test results based on color changes**
- **Labeling should include a warning when color-blindness could be an issue in reading test results**



Test System Characteristics Flex Studies Proposal

- **Waived tests must be robust, and may need to be more robust than non-waived tests**
- **Potential sources of error need to be identified, and may include, but are not limited to**
 - **Environmental conditions (temperature, humidity, altitude, etc.)**



Test System Characteristics Flex Studies Proposal

● Potential sources of error (cont'd)

- Specimen collection and handling
- Test system function and integrity (physical mishandling, dropping etc.)
- Operator error
- Sequence of reagent addition and reagent integrity
- Fluctuation in reagent volume
- Insufficient or excessive reaction times



Test System Characteristics Flex Studies Proposal

- **Potential sources of error (cont'd)**
 - Interpretation of results
 - Result reporting (results should not require calculation)
- **Studies need to demonstrate that the sources of error are controlled or mitigated**



Flex Studies Risk Assessment/Mitigation Proposal

- **As part of waiver submission, manufacturers should include information on:**
 - **Risk assessment**
 - **Likelihood of erroneous results**
 - **Measures incorporated to mitigate risk**
- **Risk assessment/mitigation information should be part of test system labeling**



Test System Characteristics Flex Studies Workgroup Discussion

- **Agreed with the proposal**
 - **Supported risk assessment and mitigation**
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Labeling – Test System Instructions Proposal

- **Format for test system labeling needs to be standardized**
- **Require labeling for all newly waived test systems to**
 - **Identify the test system as waived**
 - **Include results of waiver studies**
 - **Include a quick reference guide**



Labeling - Test System Instructions Proposal

● **Waived test system instructions need to be**

- **Clear**
- **Easy to understand**
- **Readable font**
- **Written at no higher than a 7th grade
level**



Labeling - Test System Instructions Proposal

**• Waived test system instructions
are to include**

- **Step-by-step instructions and visual aids that address**
 - **Device or test system operation**
 - **Test performance**
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Labeling - Test System Instructions Proposal

• **Waived test system instructions to include (cont'd)**

- **Analytical skills required of testing personnel**
- **Physical environment specifications or conditions for test performance**
- **Requirements for specimen collection, handling, storage and preservation**



Labeling - Test System Instructions Proposal

• **Waived test system instructions to include (cont'd)**

- **Reportable range**
- **Reference range**
- **Preparation and storage of reagents, calibrators, controls, and other materials used in testing**



Labeling - Test System Instructions Proposal

- **Waived test system instructions to include (cont'd)**
 - **Action(s) to be taken when calibration or control results not within the acceptable range**
 - **Action to be taken when the test system becomes inoperable**



Labeling - Test System Instructions Proposal

• **Waived test system instructions to include (cont'd)**

- **Performance data (include waiver study performance data)**
- **Where relevant, prevalence data and sensitivity, specificity, and predictive values**



Labeling -Test System Instructions Proposal

- **For tests waived based on home-use approval:**
 - **Require labeling to include a cautionary statement that accuracy and precision studies have not been performed in a clinical setting, unless data is provided to show otherwise**



Labeling - Test System Instructions Workgroup Discussion

- **Agreed with the proposal**
 - **For previously waived tests, allow time for revision of labeling**
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Labeling - Limitations and Intended Use Proposal

• Examples of limitations/restrictions or special considerations:

- Tests with pre- and post-analytic issues (example- genetic tests)
- Tests whose results are one component of a testing algorithm
- Tests that require public health reporting



Labeling - Limitations and Intended Use Proposal

- **Examples of limitations/restrictions or special considerations (continued):**
 - **Tests to be used in a specific geographic area or with a limited population**
 - **Seasonal testing**



Labeling - Limitations and Intended Use Proposal

- **Consider the context of testing and clinical impact when making waiver decisions because waived tests are exempt from CLIA standards and are not limited in their use**



Labeling – Limitations and Intended Use Proposal

- **Prominently display major limitations on outside of test packaging**
 - **All limitations should be included in the test system instructions and the quick reference instructions**
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Labeling – Limitations and Intended Use Proposal

- **Include a warning that failure to adhere to instructions concerning the limitations of intended use is off-label use**
- **Off-label use is uncategorized, high complexity and subject to all CLIA regulations**



Labeling - Limitations and Intended Use

Workgroup Discussion

- **Agreed with proposal, including the following manufacturers' comments:**
 - **It is not possible to list all limitations on the outside of a test kit or device packaging**
 - **Prominently display major or significant limitations**
 - **Limiting the distribution of a test as specified in the intended use is not always feasible**



Fail-safe Mechanisms Proposal

- **Fail-safe mechanisms ensure that a waived test system does not provide a result (lock-out) if test results exceed the reportable range or any component of the test system is malfunctioning**
- **Malfunctioning components could include**
 - **Device electronics**
 - **Internal/external quality control (QC) that exceeds limits**



Fail-safe Mechanisms Proposal

- **Malfunctioning components (cont'd)**
 - **Interferences that render the test unreliable**
 - **Unspecified specimen type**
 - **Calibration not performed**
 - **Environmental conditions exceeding acceptable testing conditions**



Failure-alert Mechanisms Proposal

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



Failure-alert Mechanisms Proposal

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

Workgroup Discussion

- **Agreed with proposal, with the following comments:**
 - **Lock-out feature is the ideal fail-safe mechanism**
 - **Fail-safe mechanisms are not always feasible**
 - **Failure-alert tools are critical when fail-safe mechanisms are not feasible**
 - **Risk assessment/mitigation may serve as a failure-alert**



Quality Control Proposal

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- **The manufacturer should determine the minimum frequency of external QC testing based on stress studies evaluating the following:**
 - **Lock-out features**
 - **Built-in QC**
 - **Internal process controls**
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Quality Control Proposal

- **Stress study evaluation for QC (cont'd)**
 - **Environmental (e.g. temperature) controls**
 - **Electronic QC**
 - **Sensitivity of built-in QC to analytical and test system errors**
 - **Ability to determine mishandling (e.g. dropping) device**



Quality Control Proposal

- **Stress study evaluation for QC (cont'd)**
 - **Multiple skill levels of users**
 - **Stability (e.g. shelf life) of reagents/test system**
 - **Lot-to-lot reproducibility**



Quality Control Proposal

- **Frequency of external QC testing should be specified in the test system instructions**
- **Regulatory guidance should address minimum frequency for external QC testing based on studies**



Quality Control Proposal

- **QC materials should be provided with, not necessarily in, test kits wherever feasible to increase the likelihood of QC testing**
- **When QC materials are not provided, manufacturer should include recommended sources for QC materials in package insert**



Quality Control Proposal

- **Manufacturer should recommend levels of QC materials appropriate for medical decisions**
- **QC materials should be ready to use, when possible, or require only simple preparation**



Quality Control Workgroup Discussion

- **Agreed with proposal and considered alternative methods for specifying QC testing frequency**
- **QC frequency options the Workgroup considered include**
 - Per kit
 - Per lot number/shipment
 - Per operator
 - Per specific time period



Quality Control Workgroup Discussion

• Workgroup noted the frequency might vary greatly depending on:

- Laboratory environment
 - Test stability
 - Test use
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Waiver Sales Restrictions Proposal

- **Sales restrictions may be appropriate for some waived tests. These might include any or all of the following:**
 - **Documented education and training of waived testing personnel**
 - **Ongoing assessment and documentation of competency**
 - **Criteria for pre- and post-analytic counseling**



Waiver Sales Restrictions Proposal

• Sales restrictions (cont'd)

- Establishment and documentation of a quality assurance program
- External quality assessment (proficiency testing)
- Use of test only as specified in "intended use" section of labeling
- Post-waiver surveillance and reporting of test performance



Waiver Sales Restrictions Best Laboratory Practices Workgroup Discussion

- **Workgroup agreed with the waiver sales restrictions proposal for certain tests**
- **Some proposed “sales restrictions” could be better addressed as “best laboratory practices” for laboratories performing waived tests**
- **Workgroup suggested development and promotion of “best laboratory practices” guidelines for training/education of waived laboratories**



Post-waiver Reporting/Data

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- **For all tests, FDA requires manufacturers report**
 - **Test system recalls**
 - **Medical device reporting**
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Post-waiver Reporting/Data

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- **FDA also receives input from other sources**
 - **Field inspections**
 - **Direct and indirect consumer inquiries and complaints**
 - **Government agencies**
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Post-waiver Reporting/Data

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- **Additional sources of post-waiver data and test system information**
 - **CMS complaint investigations**
 - **Studies conducted by HHS**
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Post-waiver Surveillance Proposal

- **As part of waiver submission, the manufacturer should submit and agree to follow a plan for monitoring waived test performance in actual clinical use**



Post-waiver Surveillance Proposal

- **Aspects of the surveillance could include:**
 - **Description of how to define, detect, and correct bias, imprecision, and changes in performance over time**
 - **Mechanisms for ensuring proper and consistent waived test use, and assurance of ongoing accuracy**



Post-waiver Surveillance Proposal

- **Aspects of the surveillance (cont'd)**
 - **Confirmation that fail-safe/failure-alert mechanisms are functioning**
 - **Provision for training and retraining waived testing personnel**
 - **Periodic reporting to the FDA and periodic test system review**



Post-waiver Surveillance Proposal

- **Potential aspects of surveillance reporting (in addition to currently reported information)**
 - **Field results for quality control**
 - **External quality assessment results (proficiency testing)**
 - **Common test system errors**



Post-waiver Surveillance Proposal

● Potential aspects of surveillance reporting (cont'd)

- Frequency of test system exceeding defined performance criteria
 - Design control validation information
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Post-waiver Surveillance Proposal

- **Potential aspects of surveillance reporting (cont'd)**
 - **Published reports of test system performance**
 - **Annual submission of current labeling**



Post-waiver Surveillance Proposal

- **All waived test systems should be subject to minimum monitoring/surveillance**
- **Risk assessment may be used to identify waived tests subject to more stringent surveillance**



Post-waiver Surveillance Proposal

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- **Possible basis for more comprehensive monitoring**
 - **Risk of harm to patient**
 - **Risk of harm to public health**
 - **Risk of an erroneous result**
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Post-waiver Surveillance Proposal

- **If post-waiver surveillance deviates from information and performance data submitted for waiver approval, test system is subject to re-classification from waived to moderate or high complexity**
- **Failure to comply with post-waiver surveillance and reporting requirements may result in loss of waived status for a test system**



Post-waiver Surveillance Workgroup Discussion

- **Manufacturers expressed concern about their role in surveillance implementation because they often have little or no contact with end-users**
- **Workgroup supported FDA's new *Labsun* surveillance network**



Post-waiver Surveillance Workgroup Discussion

- **Agreement that waived testing surveillance is needed, but concern about who is responsible for surveillance**
- **Recognition that post-waiver surveillance is the shared responsibility of manufacturers, laboratories and government**



Post-waiver Surveillance Workgroup Discussion

- **Surveillance of waived tests is preferable to passive event reporting to FDA by manufacturers**
 - **Surveillance is especially critical in waived laboratories that may have no system of monitoring test performance**
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Workgroup Summary

- **Productive discussion with general agreement on most issues**
- **Support for post-waiver surveillance being the shared responsibility of manufacturers, laboratories, and government, but specific roles were not defined**



Workgroup Summary

- **Acknowledged manufacturers' limited ability to control how waived tests are used**
- **Recommended development of non-regulatory guidelines addressing best practices for waived test use**