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CLIA Waivers and Coming Regulatory Reforms to Improve POCT Access

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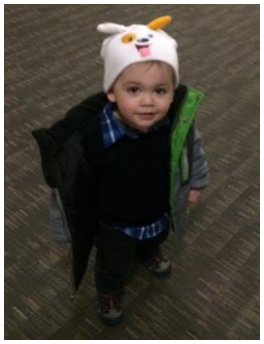
Presented by



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Agenda

A. The Importance of Point-of-Care Testing

B. The Fundamental Question

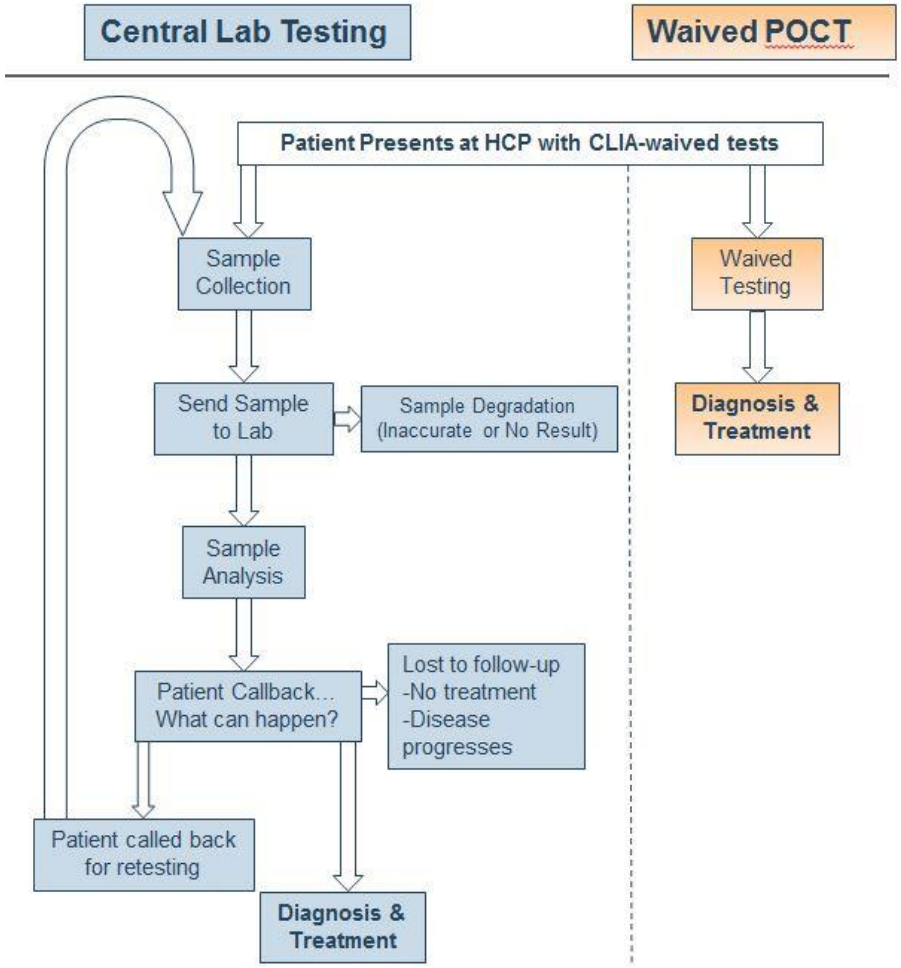
C. The Current CLIA Waiver Framework

D. The History of the CLIA Waiver Law

E. Improving the CLIA Waiver Process

The Opinions Expressed Herein Are My Own

Promise of Point of Care Testing



- ~70% of all testing facilities are Certificate of Waiver ("CoW") Labs
- CoW labs represent the vast majority of POCT sites
- By law, CoW labs can *only* perform CLIA-waived tests
- ***Conclusion: The CLIA Waiver Process Is Essential to Patients Receiving the Full Benefits of POCT***

How would you determine if a test can be run in a Certificate of Waiver Lab?

Assume You Start With The Following Common Scenario

- A study is done with lab experts running an Rx IVD in their laboratory
- FDA clears or approves the test with "moderate complexity"
  - FDA has decided the test *performance* is safe and effective for its clinical use
- It doesn't matter where the test is performed *provided* the performance is comparable that found to be safe and effective by FDA

Starting with a blank slate, how would answer whether CoW labs can use the test as well as moderate complexity labs in the study?

How can you determine if a test can be run in a Certificate of Waiver Lab?

Focus on key differences between the study environment & CoW labs (e.g., personnel)

1. You want to see if the test is simple enough to use that you don't have to be a lab expert to know how to use it
   - CoW facilities don't usually have lab experts
   - Use well-established human factors testing standards to evaluate simplicity
2. You want to have some confirmation that the results you get from the test (its accuracy) won't change going from one setting to another
   - The straightforward approach is to conduct agreement studies
     - Give samples to an expert laboratorian in their lab and group of CoW users in their facilities
     - Compare the results they get
   - If the results are comparable you have shown results aren't affected going to the CoW setting, and there is no reason to keep the test out of that setting.

Current Framework

- Has Element 1: Calls for human factors analysis / ease of use ✓
- Has Element 2: Compares agreement of trained and untrained users ✓

But there is something else too

- Element 3: Compare the test against a "reference method" to evaluate inherent accuracy
  - Doesn't tell you more about simplicity than Element 1
  - Doesn't tell you more about agreement than Element 2
  - Inherent accuracy would already have been considered as part of the premarket review (unless there is parallel review)

Current Framework: Quantitative Tests

- Allowable Total Error
  - If the question is about the user, why are we looking at *total* error?
  - What about imperfect reference standards?
- Very tight criteria
  - A cleared/approved test may not meet that criteria in the hands of *trained* users
  - A few errant results (as judged by an imperfect reference test) can sink a waiver
- Not much allowance for banked or contrived samples
  - If tests are simple to use, do you really need to use samples collected from patients?

How many quantitative tests have been waived recently?

Current Framework: Qualitative Tests

- 120 (+) and 120 (-) subject samples
  - Much higher for certain low prevalence diseases and certain analytes, like HIV
  - 95% agreement, 89% Lower Confidence Bound (per guidance)
- 60 weak (+) and 60 weak (-) contrived samples
  - 20 (+) and 20 (-) at 3 sites
  - Per guidance: have 95% agreement (on + and -) with reference method, and cannot have disproportionate results at one site, which leaves little room for error, e.g.,

Site 1 (+)	Site 2 (+)	Site 3 (+)	(+) win?
19/20 (95%)	19/20 (95%)	19/20 (95%)	Yes
19/20 (95%)	19/20 (95%)	18/20 (90%)	No
20/20 (100%)	20/20 (100%)	17/20 (85%)	No

Is the 2008 Guidance Implementing the Law Correctly?

Revisiting the Past

- CDC ran the CLIA waiver program in the 1990s and focused on inherent accuracy, similar to FDA
  - This led to various problems
- Through FDAMA 1997 Congress amended the law to clarify inherent accuracy isn't the question with CLIA waivers
  - Amended the text of the statute to qualify "accuracy" with "by the user"
  - Explained in its Committee Report:

The bill clarifies that this criteria [for a waiver] should focus on the test performance "by the user" and the potential for operator error in performing the test. . .. Without the clarifying "by the user," interpretations of "erroneous results" and "accurate" could include the inherent clinical [accuracy] of a test system, parameters that are properly reviewed [in] determining whether to approve or clear a product for marketing.

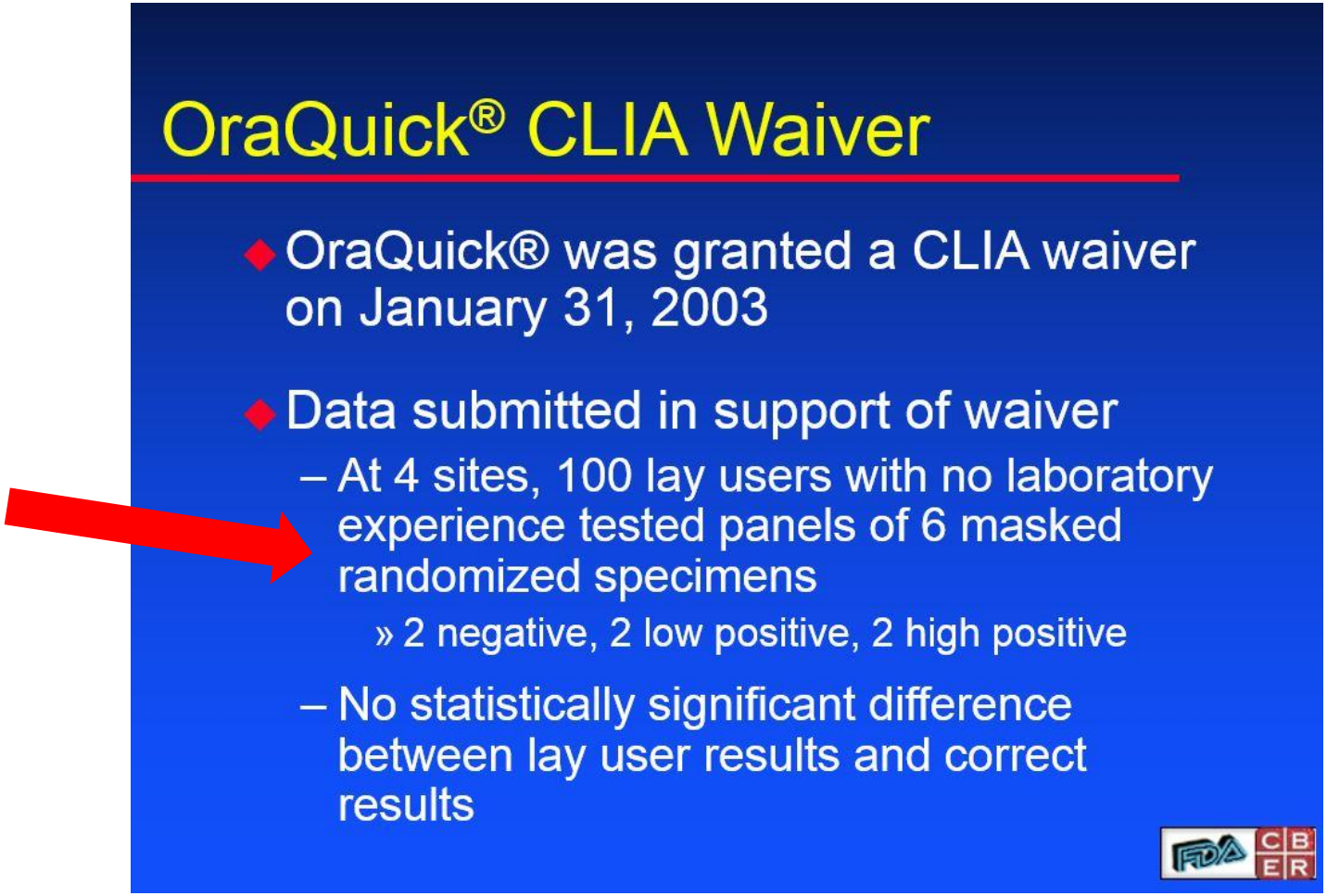
FDA's 2001 Draft Guidance

"Based on the legislative history and ['by the user'] language [a test is] 'accurate' if it performs the same in the hands of untrained users as it does in the hands of laboratory professionals when using the device under realistic conditions."

The 2001 Guidance did several things right:

- Consistent with Congressional Intent
- Recommends Agreement Studies and Straightforward Statistics
- Has Flexibility Regarding Samples
- No Reference Method or Inherent Accuracy Requirements – *Focus is on the User*

How did CLIA Waiver Studies Look Before 2008?



New Generation HIV Tests (Two 2014 Waivers)*

**Note data may include data required for PMA approvals*

Study for Test 1: 17 Untrained Users + Comparator Method

Study Population	Number of Subjects	Positive Percent Agreement	95% Confidence Interval	Negative Percent Agreement	95% Confidence Interval
HIV Status Unknown	818	96.3% (26/27)	81.7% - 99.3%	99.5% (787/791)	98.7% - 99.8%
Known HIV-1 Positive	276	98.5% (270/274[1])	96.3% - 99.4%	N/A	N/A
Total	1094	98.3% (296/301)	96.2% - 99.3%	99.5% (787/791)	98.7% - 99.8%

Study for Test 2: 53 Untrained Users + Comparator Method

Study Population	Number of Subjects	Positive Percent Agreement	95% two-sided Confidence Interval	Negative Percent Agreement	95% two-sided Confidence Interval
HIV Status Unknown	1730	93.8% (30/32)	79.9% - 98.3%	99.6% (1692/1698)	99.2% - 99.8%
Known HIV-1 Positive	745	99.9% (744/745)*	99.2% - 100%	N/A	N/A
Total	2475	99.6% (774/777)	98.9% - 99.9%	99.6% (1692/1698)	99.2% - 99.8%

Why the Change in 2008?

- Change was prompted by concerns over non-laboratorians running tests
  - CMS, CDC & CLIAC laboratorians wanted an experienced hand for all tests
  - Concerns about problems getting test results in a CoW environment
- But, these are old concerns
  - Don't account for modern "ease of use" standards, failsafes and safe guards
  - Unclear if the are relevant to modern tests in the modern environment
- The old concerns don't acknowledge that bringing modern test designs to users would help address concerns
- **Most importantly**, the inherent accuracy requirements is unrelated to the concern
  - It only works by limiting access to new CLIA-waived tests

CLIA Waivers Today

- Recognition of Importance Growing
- Advocacy by Various Organizations Increasing Focus on Needed Changes
  - Coalition for CLIA Waiver Reform
  - AdvaMedDx
  - Treatment Action Group/ACT UP New York
  - National Coalition of STD Directors
  - CDC (HIV Prevention Group)
  - and others
- ***FDA is required, by law, to revise its current guidance***

Changes Coming!

21st Century Cures Call for New CLIA Waiver Guidance

- Senators Burr and Franken introduced bipartisan legislation in the Senate as the Medical Device Innovation Act calling for revised guidance
  - ***"FDAMA clarified that the standards for such waivers should focus on the effect that the user has on results, such that if a test performs the same in the hands of untrained users as it does in the hands of laboratory professionals, then it may be administered in CLIA-waived labs (e.g. a doctor's office). . . By applying this kind of user-focused regulatory approach, more diagnostics can be performed at the point-of-care; thereby expanding patient access to these important tests and encouraging further innovation in such technologies."*** *– Statement Accompanying Bill's Release*
- That proposal was incorporated in 21st Century Cures
  - ***"[The] bill will require FDA to update guidance on certain tests performed in doctors' offices to ensure that the guidance on this matter aligns with the FDA Modernization Act's intent that, if the results by trained and untrained users are comparable, a test is considered to be accurate for CLIA waiver purposes."*** *– Senator Burr, Congressional Record*

Changes Coming!

New Draft Guidance on It's Way

- FDA is required to release –
  - Draft CLIA Waiver Guidance by December 13, 2017
  - Final CLIA Waiver Guidance by December 13, 2018

It is critically important that all stakeholders with an interest in point-of-care testing weigh in on this issue!

- For Updates on Status you can Check www.cliawaiverreform.org, FDA's website, or the Federal Register

What *should* the new guidance look like?

Getting back to FDAMA

- The intent of Congress is that FDA get back to FDAMA – how do they do this?
  - The premarket review process (510(k), PMA) determines what constitutes adequate performance (e.g., total accuracy that is adequate for a given indication).
  - The CLIA waiver process is intended to assess whether that level of performance is *maintained* when moving from a "trained" to "untrained" user setting.
- The focus of the CLIA waiver review process needs to return to the user
  - Focus on Human Factors / Usability (test simplicity)
  - Focus on ability to of train and untrained users to get comparable results
    - Agreement studies
    - Testing with split contrived samples in appropriate simulated settings
      - *Clinical / analytical issues with real samples are addressed in the 510(k)/PMA review process. This does not need to be revisited in CLIA waiver studies, so why not use contrived samples?*

Focus on Human Factors

- The really focus of POCT testing needs to be on human factors – can untrained users successfully use the test?
  - Today, FDA often conflates the "simplicity" requirement with "accuracy"
  - It is simplicity that key
- Human factors testing is well-accepted throughout the rest of CDRH
  - FDA Guidance for Industry: Applying Human Factors and Usability Engineering to Medical Devices (Feb. 2016)
  - Verifying that untrained users can use test as well as trained users can be done best through these focused, validated studies, not clinical trials

Alternative Study Design Concepts: Quantitative

- Agreement Studies
  - Samples of unknown concentration
    - Must achieve a range of results
    - Can supplement with banked or contrived samples
  - One trained and one untrained user takes a patient measurement
  - The trained user population is compared to the untrained user population
  - "Limits of Agreement" are developed based on inherent test performance, etc. (Bland and Altman, Stat Methods Med Res 1999; 8; 135-160)
- Assessment of Accuracy Equivalence
  - Use all contrived/banked samples of known concentration
    - No subject samples collected
  - Each user (trained and untrained) analyzes each sample
  - Limits of agreements for user accuracy are developed, and trained & untrained populations are compared

Alternative Study Design Concepts: Qualitative

- Hybrid Agreement Study
  - Study with Subjects
    - Find 120 (+) and 120 (-) subjects (all comers) as determined by test with trained users
    - Calculate agreement and apply reasonable, risk-based "win" criteria, e.g., minimum agreement of 90%, and a lower confidence bound in the range of 80%
  - Study with contrived weak (+) and weak (-) samples
    - Prepare 60 (+) and 60 (-)
    - Achieve reasonable proportionate agreement across sites (e.g., 85%)
- Assessment of Accuracy Equivalence
  - Each untrained and trained user evaluates a set of contrived or banked samples of known concentration
  - Sensitivity and specificity is calculated
  - Squared difference between trained & untrained users does not exceed the expected value of the squared difference between trained users by a predetermined, risk- and tech-based margin

Strategies for Working in the Current System

In the interim, how do we overcome problems with the 2008 Guidance?

- Help FDA and others understand the public health need
  - Waived tests can help patients
  - Waived tests can improve the public health
  - Communicate to FDA and the public about the need for tests
- Understand the current waiver environment
- Propose sensible, scientifically sound alternatives to aspects of studies that cause problems
  - Guidance is *guidance*, not law
- Get back to basics – **FDAMA** (which *is* the law)

Appeal Adverse Decisions

- Every CLIA Waiver applicant has the right to appeal adverse decisions
  - 21 C.F.R. § 10.75 – Internal Agency Review of Decisions
  - Center for Devices and Radiological Health Appeals Processes - Guidance for Industry and Food and Drug Administration Staff (May 2013)
- Take appeals above the OIR to CDRH Management
  - CDRH management has encouraged innovation
  - CDRH management has recognized the importance of access in healthcare (e.g., mobile medical app policies)
  - CDRH management understands the value and ability of human factors testing to validate product use
- Management has an appeals process for a reason – use when necessary

In Closing…

- Keep the focus on patients
  - These tests *help* patients, and never lose sight of that
- Keep pressing for reforms – **COMMENT ON THE DRAFT GUIDANCE & STAY ENGAGED!**
- Keep proposing sensible solutions where the current framework just won't work effectively to bring patients the tests they need

- If you have questions, please feel free to contact me
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  - www.cliawaiverreform.org