FDA's CLIA Waiver Approval Process and Criteria

Prakash Rath, Ph.D.
Food and Drug Administration
Office of *In Vitro* Diagnostics and Radiological Health (OIR)

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Outline

- Background: CLIA waivers and waived devices
- Case study 1: Blood Glucose Meters
- Case study 2: Hematology Analyzers
- Current issues and challenges
- CLIAC discussion

Clinical Laboratory Improvement Amendments (CLIA)

- Three federal agencies regulate CLIA
  - Center for Medicaid and Medicare Services (CMS),
  - Center for Disease Control (CDC), and the
  - Food and Drug Administration (FDA).

- Each agency has a unique role in assuring quality laboratory testing

FDA's Role CLIA Categorization

- FDA grants clearance or approval, under FFD&C Act, according to risk based on intended use:
  - Class I - low risk, usually exempt from premarket review
  - Class II - moderate risk, requires "substantial equivalence" to predicate device (510(k) clearance)
  - Class III – high risk intended uses, require premarket approval (PMA)
- After clearance/approval, the reviewer performs a CLIA categorization based on predefined complexity score and/or regulation.
- Sponsors with premarket exempt devices should request FDA for their test to be CLIA categorized.

Waived Test Definition

The statutory criteria are defined under 42 U.S.C. § 263a(d)(3) :

"…[L]aboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the [Health and Human Services] Secretary, are *simple* laboratory examinations and procedures that have an *insignificant risk of an erroneous result*, including those that – (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly." [Emphasis added].

Pathways for CLIA Waived Categorization

1) By Regulation – 42 CFR 493.15(c) for 9 generic tests

   Example: for urine: pregnancy, glucose, hemoglobin (for details, see regulation)

2) By FDA Clearance or Approval for home use or OTC

   Example: OTC glucose meter (fingerstick)

3) By meeting the statutory criteria

   - via CLIA Waiver Guidance (Application Process)

   Example: Flu test

How does a test system meet the CLIA waiver guidance criteria?

- Is the test system simple?

- Does the test system have an insignificant risk of an erroneous result?

How do you demonstrate “Simple”?

- Fully automated instrument or unitized test system
- Uses direct unprocessed samples – finger stick blood or venous whole blood or urine
- Non-technique dependent specimen or reagent manipulation
- No operator intervention during analysis
- No technical or specialized training – troubleshooting or complex error codes
- Easy to read test results (pos, neg, value, etc.)
- Clear labeling

Labeling for Waived Test (according to the CLIA waiver guidance)

- Quick reference instructions at 7th grade reading level
- Procedural steps at 7th grade reading level
- Includes QC recommendations for use of external ready to use QC materials and for frequency of testing
- Educational information

How do you Demonstrate "Insignificant Risk of Erroneous Result"?

- Risk Analysis (identification of all potential sources of error and how to mitigate their risk)

- Test Failure Alerts and Fail-Safe Mechanisms validated through flex studies

Risk Analysis

- Operator error/human factors
- Specimen handling and integrity – clotted specimen, short sample, interfering substances
- Reagent integrity – storage, outdated
- Hardware, software and electronics integrity - power failures, bugs, physical trauma to unit
- System stability - calibration
- Environmental factors – heat, humidity, electrical or electromagnetic interference

Fail-safe and Failure alert mechanisms

- Lock-out features
  - No result if expired reagents
  - No result if internal electronic checks fail
  - No result if QC fails
- Physical features
  - Strip and cartridge are in correct placement
- Monitors of the environment
- External QC materials
- Internal procedural controls

Demonstrating "Insignificant Risk of Erroneous Result" - "Accuracy"

- The term "accurate" tests refers to those tests that are comparable to traceable methods (trueness).
- Prospective clinical studies of the device proposed for waiver:
  - intended clinical testing sites (min. 3 sites)
  - intended operators (min. 9 intended operators)
  - intended sample type and matrix (see guidance)
  - testing over time, as in typical intended use setting (min. of 2 weeks)

Issues Before CLIAC

- Technology is increasing the number of devices that can be automated and easy to use
- Increasing access and speed of diagnostic devices would allow for better patient management
- Proper labeling is crucial for controls of waived devices
- Will present two case studies that point to what we call the clearance-categorization-conundrum to illustrate the current pain points of CLIA waived devices as they are used and in the waiver by application process.

The Clearance-Categorization-Conundrum for CLIA waived tests

What is the intent of CLIA waived tests according to the FDA CLIA waiver guidance?

- Waived tests are intended for waived settings (i.e. those without routine regulatory oversight on quality standards)
- This waived test should only be used in strict compliance with the manufacturers' instructions, for the cleared intended use specified on the label
- The performance criteria for waived tests have been evaluated and tested:

  1) CLIA waived sites, 2) in intended use population (patients),
  3) by operators from intended use CLIA waived sites
  4) in intended use sample matrices

The Clearance-Categorization-Conundrum for CLIA waived tests (cont.)

What are the issues and concerns with CLIA waived tests?

- CLIA waived tests are sometimes used not as intended

  Example: A test used outside its labeled intent.

  - sometimes waived devices are used in different intended use populations in which the device has never been evaluated or tested (e.g. critically ill patients, patients undergoing chemotherapy, or neonates)

  - Sometimes waived devices are used with samples in which the device has not been evaluated

Case Study:

Blood Glucose Meters (BGM)

Case study : Blood Glucose Meters

What is the impact of BGMs having a CLIA waived status?

- **What?** Class II devices (moderate risk) that require 510(k) clearance prior to marketing. BGMs are categorized as 'waived' by regulation, not application.
- **End user population?** Intended for diabetics at home. However, it is used for critically-ill patients
- **Healthcare setting?** Intended for home use, but used in hospitals, nursing homes, physicians offices, ER's.
- **Who performs the test?** Intended for self-monitoring by lay person, but has been used in POC by professionals

Case study : Blood Glucose Meters (cont.)

- **Issue?** Manufacturers typically seek clearance for OTC use, but the majority of meters are being used in professional settings (in which they have not been validated for)

- **Bubble?** Numerous groups have called for improved accuracy and criteria because patients are being put at risk. Glucose meters account for the most device adverse event reports to the FDA (>25,000/year)

Case study : Blood Glucose Meters (cont.)

- **Result?** FDA held public meeting on BGMs in 2010. Called for standards based on OTC or POC use, and the need for better accuracy and performance.
  - FDA issued 2 draft guidance documents in Jan 2014
    - Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use
    - Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use
- The Comment period closed May 7, 2014
- FDA currently analyzing all comments provided on the documents

Case Study:

Hematology Analyzers

Case study: Hematology Analyzer

What is the impact of these devices not having a CLIA waived status?

- **What?** Class II devices (moderate risk) that require 510(k) clearance prior to marketing
- **End user population?** Indicated for use for quantitative determination of white blood cell (WBC) count in capillary or venous whole blood.
- **Healthcare setting?** Intended for use in clinical laboratories and for point-of-care settings
- **Who performs the test?** Professional health care workers

Case study: Hematology Analyzer (cont.)

- **Issue?** The company wanted to demonstrate that HemoCue WBC System is simple to use and accurate in the hands of the intended operators and that there is an insignificant risk to obtain an erroneous result.

- **Bubble?** There is a need for hematology analyzers in rural settings (most likely CLIA waived sites), and the benefit/risk was not favorable (and the application was denied).

Case study: Hematology Analyzer (cont.)

- **Result?** The FDA brought the Hemocue CLIA Waiver to a the Hematology and Pathology Advisory Panel in 2009. The waiver was denied and the briefing document states 'The value of accurate laboratory test results in a least burdensome setting is the underlying premise of the CLIA waiver program for laboratories and devices. It is easy to describe circumstances in which the availability of even limited information, such as WBC alone, would increase the speed, efficiency and even outcome of management for some patients. It is also easy to describe circumstances in which technology that is limited in scope and performance, used in lieu of more comprehensive and robust methods, can lead to therapeutic misadventure for some patients.'

Case study: Hematology Analyzer (cont.)

- **Issue?**
  - FDA clearance was for a broad intended use
  - Clear clinical use in waived setting was within a narrow context
  - Given the only control is labeling, FDA's approach is to request clearance/approval within a narrow intended use that may include training

Summary of Issues

- The only control in a waived setting is labeling
- Some waived settings may have user training or other controls that may help mitigate risks, but may not be able to meet requirements for a moderate complex, or high complexity CLIA laboratory
- Labeling may not be sufficiently narrow to mitigate risks

Discussion and Questions:

- How can manufacturers mitigate the risk of unintended use in a CLIA waived setting?
- How can CLIA waived laboratories mitigate the risk of unintended use?
- How can the FDA, CMS and CDC mitigate the risks of unintended use?

Discussion Questions (cont.):

- Besides modifying the labeling, is there anything else the FDA, CMS, and CDC do to ensure testing in waiver settings is being performed adequately?

Thank you!
Questions?

- For CLIA related questions please email:

CLIA@fda.hhs.gov

Prakash.Rath@fda.hhs.gov

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For more information of CLIA at the FDA, please checkout our updated webpage

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm

References

- **CLIA Waiver by Application Guidance Document**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm
- **CLIA public database**
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm
- **Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use Guidance Document**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380325.pdf
- **Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use Guidance Document**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380327.pdf