Recommendations for CLIA Waiver Applications for Manufacturers of In Vitro Diagnostic Devices

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CLIA Waiver Background

- CLIA categorizations are determined by FDA as part of the 510(k)/PMA process
- CLIA category is based on technology of predicate or similar test systems
- Most IVD test systems are assigned CLIA categories of moderate or high complexity based on the original CDC rules- waived tests are a special case.

3 Routes to CLIA Waiver

- FDA cleared for home use
- Waived by regulation- 9 tests
  - Urine dipsticks, urine pregnancy, urine ovulation tests, fecal occult blood, spun hematocrit, hemoglobin by spun hematocrit, sedimentation rate, glucose meters cleared for home use, hematocrit by Hemocue (added later)
- Waiver Petition- simple technology and low likelihood of an erroneous result

CLIA Waiver by Petition

- 4 primary aspects
  - Conformance to test system characteristics
  - Field study data
  - Risk analysis
  - Labeling considerations

CLIA Waiver Test Characteristics

- Need to show conformance to prescribed elements
  - Logical requirements
  - See Page 8 of FDA Guidance Document
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf

CLIA Waiver Studies-1

Accuracy

- Enroll 3 “typical” CLIA waived sites (MD offices, clinics, etc.)
- Target 3 typical operators per site (9 total, nurses, nursing assistants, office managers)
- Operators must perform testing solely by following written instructions
- At the end of study, demographic survey and questionnaire to be completed by each operator

CLIA Waiver Studies-2

Accuracy (continued)

- For quantitative tests, each site must collect a minimum of 120 comparative results- attempt to span dynamic range, but up to ~15% of samples may be prepared/manipulated.
- POC test is performed in a blinded fashion; comparative/reference test is performed in a blinded fashion, preferably at a central lab.
- Results are compared side-by-side, comparative test is “right,” by definition.

CLIA Waiver Studies-3

Accuracy (continued)

- For qualitative tests, 2-step process
- Step 1 is similar to quant tests- across 3 sites, 9 operators perform testing to satisfy 120 pos and 120 neg results, compare to established method
  - Each operator should observe 5 pos and 5 neg
- Step 2 focuses on performance around the cutoff

CLIA Waiver Studies-4

Accuracy (qualitative continued)

- Sponsor prepares 60 aliquots of “weak positive” and “weak negative”
- A weak positive is reported as “positive” 95% - 99% of the time by trained personnel- same rule for weak negative
- The aliquots are distributed to 3 sites and tested in a blinded fashion and random order

CLIA Waiver Studies-5

Accuracy (continued)

- **Data requirements - Quantitative**
  - 95% of the results must be within the ATE (allowable total error), and 100% of the results must be within the LER (limit of erroneous result)
  - The ATE and LER are determined on a case-by-case basis, largely driven by proficiency testing limits set up by CMS
  - Suggested limits may be 10% ATE, and 15% LER
  - ATE and LER are established before testing begins

CLIA Waiver Studies-6

Accuracy (continued)

- **Data requirements - Qualitative**
  - For Step 1: 95% of the results must be correct
  - For Step 2: 95% of the results must be correct for each category of weak positive and weak negative, i.e., minimum of 57/60 correct for each type

CLIA Waiver Studies-7

Accuracy (continued)

- Logistics to be considered:
  - Choice of comparative/reference method (FDA has an opinion- need “highest order”)
  - Sample stability is very important if option of central lab is chosen
  - Need to pre-qualify comparative method, central lab (if applicable), and reference technologists- recommend a pilot study

CLIA Waiver Studies-8

* Precision- Quantitative Tests

- Each site must perform precision testing to confirm precision in the hands of the ultimate user (CLIA waived site)
- Testing protocol to be established based on sample type and sample stability
- Typical protocol is 3 levels, tested over multiple days by multiple operators
- %CVs should be similar to %CVs when tested by trained operators

* not in guidance document

Risk Analysis CLIA Studies

- Risk mitigations- stress studies for procedural steps
  - First there is a risk analysis, followed by flex studies
  - Artificially simulate potential risks
- Concentrate on areas prone to errors or failures
  - Impact of not following procedural directions
  - Deviations in environmental conditions
  - Result interpretation

Waived: Labeling Issues

- Quick Reference Guide in addition for User Manual and Package Inserts
- Wide use of diagrams
- Clear instructions
- Reading grade level at 7th grade (Flesch-Kincaid Reading Program, part of MS Word)

Q&A #1

- Q: What kind of questions go into the CLIA operator survey?
- A: The survey focuses on the ease/difficulty of the procedural steps and the labeling.
  - It is recommended that this is done using a 4 or 5 point Likert scale where each step is queried as to whether is was, “easy, somewhat easy, neutral, somewhat hard, or hard.”

Q&A #2

- Q: What are proficiency testing limits and how are CLIA limits chosen?
- A: Proficiency testing (PT) limits are established by CMS and they dictate the result tolerance, e.g., ±15%, for each analyte that is offered by that lab. PT is performed 3x/year with 5 “unknowns” for each analyte in order to maintain CLIA certification.

Q&A #3

- Q: What is the impact of performing 510(k) and CLIA waiver studies at the same time?
- A: It is possible, but careful planning is needed. The studies must be set up to meet the more stringent CLIA rules regarding personnel, training, and “goodness” of the data.

  Still need separate filings (User Fees).

Q&A #4

- Q: What are the labeling requirements beyond those for a non-waived test?
- A: Waived labeling must include a quick reference guide that clearly shows the procedural steps in simple English; diagrams along with the text are encouraged.

Q&A #5

- Q: What pre-training can be done at the CLIA waived sites?
- A: The sites may be trained on: subject enrollment and informed consent (if needed), sample processing for reference testing, reference testing, and completion of the paper work. Sites may not be trained on the CLIA waived method under consideration.

Q&A #6

- Q: What is a good way to handle risk analysis in a CLIA waiver petition?
- A: First, we should identify those risks associated with the *operator*. (This is different from risk analysis for the entire system.) This is Tier 1, according to the guidance document. Then we described how we mitigate or eliminate those risks (Tier 2), as documented by flex studies.

Q&A #7

- Q: Do the IDE exemptions apply for CLIA waiver studies?
- A: Yes. As the results from the CLIA waived studies are not used for clinical management, and since the in-vitro mature of the sample collections still applies, no IDE is required to perform CLIA waived studies.

Q&A #8

- Q: What are the rules for QC testing of CLIA waived IVDs?
- A: FDA most frequently requires that QC testing be performed (1) at least every 30 days, (2) with every new operator, (3) with every new lot of material, (4) with every new shipment, and (5) whenever laboratory conditions have changed.