What’s New in Quality & Regulatory Expectations?

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Disclosures

Relevant Financial Relationship(s):
Nothing to Disclose

Off Label Usage:
Nothing to Disclose
Objectives
1. Review top 10 CLIA deficiencies
2. Review updates to interpretive guidelines
3. Discuss recent FDA actions with pharmacogenetics testing
4. Discuss potential FDA oversight of lab-developed tests

Top 10 CLIA Deficiencies (October 2018)
493.1252(b) – Equipment, instruments, reagents, materials, supplies
The laboratory must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. The criteria must be consistent with the manufacturer's instructions, if provided. These conditions must be monitored and documented.
Top 10 CLIA Deficiencies (October 2018)

493.1252(b) – Equipment, instruments, reagents, materials, supplies

- Define, monitor, and document conditions
  - Water
  - Temperature
    - What is ‘refrigerate’? What is an actionable limit?
  - Humidity
    - This can be very tricky...
  - Electrical current

Top 10 CLIA Deficiencies (October 2018)

493.1252(d) – Reagent Quality

Reagents, solutions, culture media, control materials, calibration materials, and other supplies must not be used when they have exceeded their expiration date, have deteriorated, or are of substandard quality.
Top 10 CLIA Deficiencies (October 2018)

493.1252(d) – Reagent Quality

• If it’s expired, throw it away
  - “This reagent is expensive” does not magically increase stability beyond the manufacturer’s expiration date

• Best practice: document expiration date on the bottle or a log
  - Periodic sweeps through the lab looking for expired reagents

• A new expiration date must be recorded if opening the container changes the expiration date (CAP COM.30250)

• Reagents without expiration dates should have one assigned (CAP COM.30400)

Top 10 CLIA Deficiencies (October 2018)

493.1236(c)(1) – Proficiency Testing

At least twice annually, the laboratory must verify the accuracy of any test or procedure it performs that is not [a regulated analyte]
Top 10 CLIA Deficiencies (October 2018)

493.1236(c)(1) – Proficiency Testing

- Purchase proficiency testing material from a 3rd party
- Utilize alternative proficiency assessment
  - Specimen exchange with another laboratory (split samples)
  - Blinded testing of previous specimens or QC material
  - Patient pool
  - Clinical correlation/chart review

Refer to CLSI GP-29A2 Assessment of Laboratory Tests When Proficiency Testing is Not Available

Top 10 CLIA Deficiencies (October 2018)

493.1235 – Personnel competency assessment

As specified in the personnel requirements in subpart M, the laboratory must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency.
Top 10 CLIA Deficiencies (October 2018)

493.1235 – Personnel competency assessment
• Competency must be assessed if someone is performing testing and/or reporting results
  ◦ Regardless of role (i.e. includes technical/clinical consultants)
• Have a competency policy and follow it
  ◦ Based on the individual’s responsibilities
  ◦ Must include the six required elements for competency

Top 10 CLIA Deficiencies (October 2018)

493.1289(a) – Analytic systems quality assessment
The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems
Top 10 CLIA Deficiencies (October 2018)

493.1289(a) – Analytic systems quality assessment

- What mechanisms do you have in place to catch problems?
  - Quality Control
  - Temperature monitoring
  - Verification/validation

- What do you do about problems once they’re identified?
  - Document (e.g. nonconforming event management)
  - Process improvement methodologies (e.g. PDSA)

- How do you ensure issues don’t reemerge?
  - Effectiveness checks

Top 10 CLIA Deficiencies (October 2018)

493.1251(a) – Procedure manual

Written procedure manual for all tests, assays, and examinations performed by the laboratory must be available to, and followed by, laboratory personnel.
Top 10 CLIA Deficiencies (October 2018)

493.1251(a) – Procedure manual

- ‘Written’ could mean on paper or electronic
  - Must be accessible
  - Hand scribbled notes ≠ ‘a procedure’ [reference 1251(d)]
- Procedures are not optional
  - “Do you want to know what the procedure says, or what we actually do?”
  - Make sure people doing the work are involved in procedure updates
    - Procedure should still align with verification/validation requirements

Top 10 CLIA Deficiencies (October 2018)

493.1251(b) – Procedure manual

The procedure manual must include the requirements for patient preparation; specimen collection, labeling, storage, preservation, transportation, processing, and referral; and criteria for specimen acceptability and rejection
Top 10 CLIA Deficiencies (October 2018)

493.1251(b) – Procedure manual

- Procedure tells your staff what they should do and what they can’t do
  - If it’s not in the procedure, there’s no way to know what’s right
- Rejection criteria: collection tube, temperature, collection date, lipemia, hemolysis, etc.
  - Based on validation
- Process steps, quality control & calibration
- Reporting steps, reference intervals, alert values

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Top 10 CLIA Deficiencies (October 2018)

493.1291(c) – Test report

The test report must indicate the following: for positive patient identification, either the patient’s name and identification number, or a unique patient identifier and identification number, the name and address of the laboratory location where the test was performed, and other requirements specified in 493.1291(c).
Top 10 CLIA Deficiencies (October 2018)

493.1291(c) – Test report

• Labs with multiple sites must identify the site where each test was performed (method determined by the lab)
• Test results
• Reference interval (sex/age specific, as applicable)
• Genetic tests have more requirements
  ◦ Method used and mutations detected
• Documentation of rejected specimen
  ◦ e.g. Test cancelled due to gross hemolysis

Top 10 CLIA Deficiencies (October 2018)

493.1254(a)(1) – Maintenance and function checks

Maintenance as defined by the manufacturer and with at least the frequency specified by the manufacturer.
Top 10 CLIA Deficiencies (October 2018)

493.1254(a)(1) – Maintenance and function checks

• Maintenance requirements in the package insert and/or user manual are the bare minimum
  - Potential consideration prior to purchase
  - This includes non-analytical equipment like centrifuges
• Your use may warrant additional maintenance, e.g. monthly instead of quarterly
• Maintenance must be documented, whether performed by the vendor or by the lab
  - Includes date & whether acceptance criteria were achieved

Top 10 CLIA Deficiencies (October 2018)

493.1253(b)(1) – Performance specifications

Each laboratory that introduces an unmodified, FDA-cleared or approved test system must demonstrate that it can obtain performance specifications comparable to those established by the manufacturer.
Top 10 CLIA Deficiencies (October 2018)

493.1253(b)(1) – Performance specifications

• Unmodified – changing a parameter of an FDA-cleared/approved kit makes the test an LDT
• Accuracy (trueness)
  ◦ Reference materials or reference method
• Precision (reproducibility)
  ◦ Testing a known sample over time
• Reportable range (accurate lowest and highest values)
• Reference range (verify or use published literature)

CLIA Interpretive Guidelines Updates (Fall 2019)

• Updated periodically by CMS
  ◦ Identify outdated information
  ◦ Include new and updated CMS policies and procedures previously communicated via CMS memo(s)
• Provides consistency in practice and eliminates duplication for State Surveyors and Regional Offices
CLIA Interpretive Guidelines Updates (Fall 2019)

6002 CLIA Applicability (493.3) (a)(1)
- Certain types of laboratories and laboratory tests are NOT subject to meeting CLIA requirements. These include:
  - Research labs that **test human specimens but do not report patient specific results**;
  - Substance use disorder testing (such as for alcohol and/or drugs) solely for employment purposes (such as disciplinary, administrative, or legal action)

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CLIA Interpretive Guidelines Updates (Fall 2019)

6006.7 Verification of Laboratory Director Qualifications

6116.4 Record Review
- Optional use of primary source verification (PSV) to confirm personnel credentials and provide PSV documentation as evidence of compliance with the personnel requirements
- Direct observation of documents, PSV documents, or a combination of both to achieve compliance

(Subpart M)
CLIA Interpretive Guidelines Updates (Fall 2019)

• 6010 Regulatory Exceptions for a Multiple Site Certificate
  • Mobile and Temporary Testing Sites
    • Home Health Agencies and Hospice
  • Limited Public Health
  • Laboratories within a Hospital

(S&C: 12-09-CLIA and 42 CFR 493.35(b)(1)-(b)(3), 493.43(b)(1)-(b)(3), or 493.55(b)(1)-(b)(3))

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CLIA Interpretive Guidelines Updates (Fall 2019)

6016.1 Written Notification of Changes in Laboratory Operations

493.45, 493.51, 493.57, 493.63

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<td>Corporate Address</td>
<td>Change in Accreditation Organization</td>
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<tr>
<td>Ownership</td>
<td>Voluntary Closure/Termination</td>
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<tr>
<td>Specialty or Subspecialty change (Certificate of Compliance)</td>
<td>Personnel-Technical Supervisor</td>
</tr>
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</table>
CLIA Interpretive Guidelines Updates (Fall 2019)

- 6016.1 Change in Laboratory Operations - *Certificate of Accreditation Laboratories*
  - Laboratory Director and Specialty changes go through Accreditation Organization

- 6270 Failure to Furnish Notification of Changes
  - *Principal sanctions may be imposed if a laboratory fails to meet the notification of change requirements as outlined in the regulations*
  
  493.63

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CLIA Interpretive Guidelines Updates (Fall 2019)

6042 Proficiency Testing (PT)
  - PT referral rules apply regardless of certificate type if a lab enrolls and participates in PT

6276.2 Adverse Actions Based on Improper Referrals in Proficiency Testing
  - Categories 1, 2 and 3 added

  493.801
CLIA Interpretive Guidelines Updates (Fall 2019)

6116.4 Record Review
- Regents Bachelor’s Degree (RBD)
- Home schooling
- Bachelor Degree in Nursing
  - Meets bachelor’s degree in biological science requirement for high complexity testing
- Military Training

Subpart M

CLIA Interpretive Guidelines Updates (Fall 2019)

6120.1 Regulatory Compliance Decision
- Determining Immediate Jeopardy
  493.2 and 493.1812

6140.1 Counting Tests
- Only tests that are ordered and reported should be included in the laboratory’s test volume(s)
- CMS 116
CLIA Interpretive Guidelines Updates (Fall 2019)

6256.3-6256.7 Sanctions

• Principal
  • limitation, suspension or revocation of the CLIA certificate

• Alternative
  • Directed PoC, State onsite monitoring; and/or Civil money penalty

• Additional
  • Cancellation of Medicare payment approval, suspension of part or all of Medicare payment


CLIA Interpretive Guidelines Updates (Fall 2019)

6256.3-6256.7 Sanctions

• Civil Suits
  • Activities are harmful to public health

• Criminal
  • Individuals can be convicted of intentionally violating any CLIA requirement and be imprisoned or fined
CLIA Interpretive Guidelines Updates (Fall 2019)

• **6276.5 - Notice to Office of the Inspector General (OIG)**

493.1775 (b)(3)

*Within 30 days, RO informs OIG of the following:*

- The owner, operator, or lab employee is guilty of misrepresentation in obtaining a CLIA certificate;
- Perform a laboratory examination or other testing not included in the laboratory’s CLIA certificate;
- Owner, operator, or lab employee violated or aided and abetted in the violation of any CLIA provisions and its implementing regulations; or
- The lab intentionally referred PT samples to another laboratory for analysis.

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FDA Action on PGx Testing

• Pharmacogenomic testing: genetic predisposition to how well a drug is metabolized
  - Typically laboratory-developed tests, regulated by CLIA/CMS
  - FDA regulates IVD kits, using ‘enforcement discretion’ for LDTs

• FDA activity related to PGx testing
  - Fall 2018 – Safety notice regarding PGx testing
  - April 2019 – Warning letter sent to Inova Health System
  - Summer 2019 – Additional companies contacted
  - What happens next? Unclear…
FDA Regulation of LDTs

- 2014: FDA publishes draft Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

- 2017: FDA releases discussion paper noting preference for legislative approach

- 2018: Verifying Accurate Leading-edge IVCT Development (VALID) Act (discussion draft)
  - (IVCT) In Vitro Clinical Test: IVDs and LDTs under the same regulatory umbrella

VALID

- Grandfathering provision
  - Tests on market prior to passage
  - Modifications may still need to be submitted

- Classification (drives submission requirements)
  - Low risk
  - High risk
  - Rare disease (<8,000 tests/year nationwide)
  - Custom or Low Volume (5 patients/year)
  - First-of-a-Kind (based on Test Group)
VALID

• Test Group – combination of:
  ◦ Analyte
  ◦ Method
  ◦ Specimen Type
  ◦ Intended Use

• If FDA has not reviewed a Test Group combination before, the test is First-of-a-Kind (i.e. high risk)

• National test information tracked in the Comprehensive Test IT System (CTIS)
  ◦ Including grandfathered tests

VALID

• CTIS – publicly available database
  ◦ Registration of developers
  ◦ Electronic submission portal
  ◦ Test performance summaries
    ◦ This is how we’d determine first-of-a-kind
  ◦ Adverse event reporting

• Reporting events where IVCT contributed to death or serious injury and was not the result of ‘laboratory error’
  ◦ Within 5 days
VALID

• Precertification
  • Based on single technology and medical subspecialty
  • Submission of representative test packet
  • Subsequent tests under the precert could be marketed without submission to FDA
  • Renewal with new representative test every 4 years

• Both parties are relying on a viable precert program for VALID to work
  • Congress has doubts

VALID

• Modifications
  • Labs are continuously working to improve an assay

  • FDA review and approval required for:
    • Test Group changes (analyte, method, specimen type, intended use)
    • Changes to performance claims (e.g. accuracy)
    • Changes that “adversely affect performance of the test”

  • Modifications remove grandfather status of a test
VALID

• Submission Packet
  • Intended use and test system description
  • Verification/Validation summary
  • Raw data (high risk tests)
  • Prospective change protocol (as applicable)
  • Risk assessment
  • Proposed labeling

VALID

• Labeling
  • IVDs are physical ‘things’ with package inserts
  • LDTs aren’t; include information on ‘test report template’
    • Test notification number
    • Intended use
    • Instructions for reporting adverse events
    • Instructions for accessing performance data
    • Warnings, contraindications, & limitations
VALID

• CLIA overlap & duplicate regulation
  • Document management
  • Reagent handling
  • Test verification/validation requirements

• Inspections
  • High risk tests require an inspection of the test and the quality system

VALID

• Transition period (between enactment and implementation)
  • 4 years? Possibly less
    • Laboratories would need to develop new processes and practices in this time
    • Registration & listing (i.e. CTIS)

• LDTs marketed 90 days prior to enactment are grandfathered

• Anything else would require a submission once the legislation is implemented (unless exempt)
QUESTIONS & DISCUSSION